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DISTURBANCES OF BLADDER FUNCTION IN RELATION TO PREGNANCY*

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MY first duty is to thank the President and Council of the Royal College of Obstetricians and Gynaecologists for the honour conveyed by the invitation to present this Blair-Bell Memorial Lecture. It is an honour of which I am made all the more appreciative by the fact that the work on which it is based was carried out in the Unit of which Blair-Bell was formerly the head. Although occupying the Chair of Obstetrics and Gynaecology in the University of Liverpool for only ten years (1921–1931), such was the impact of his personality that Blair-Bell's influence is still felt in the department. Moreover, his restless and inquisitive spirit still pervades the hospital wards in which this research was conducted. For this is a report on an essentially clinical investigation, one concerned with the process of micturition and with its disturbances which accompany pregnancy and parturition. The common changes in bladder function seen during and immediately after pregnancy are frequency, stress incontinence and retention of urine. Of these, only the first and last form the subject of this communication. The third is to be described elsewhere.

Frequency of micturition occurring during pregnancy, and retention of urine occurring sometimes during pregnancy but mostly after labour, are well-known phenomena yet the mechanisms responsible for them are mostly matters of theory or of views hallowed by tradition rather than by proof.

* A Blair-Bell Memorial Lecture presented at the Royal College of Obstetricians and Gynaecologists, 25th September, 1959.

FREQUENCY OF MICTURITION

(1) THE OCCURRENCE AND TYPE OF FREQUENCY

Frequency of micturition during otherwise uncomplicated pregnancy is so common that it has long been regarded as a normal reaction to this physiological state. It is described as one of the four cardinal symptoms of early pregnancy. The standard teaching is that the frequency is diurnal rather than nocturnal and that it occurs mainly in the first and third trimesters. Yet it would appear that there is no published evidence to support these generalizations nor, indeed, is the exact incidence of frequency known. A series of 400 women attending a hospital antenatal clinic was therefore studied. All were personally observed throughout pregnancy and after delivery. They were selected only in so far that cases showing evidence of pre-existing organic disease of any kind, or of the development of urinary tract lesions, pre-eclampsia and hypertension during pregnancy, were excluded. Only apparently healthy women with a single normal foetus were accepted. Each was questioned in detail about urinary symptoms and each kept records of her daily voiding acts. A group of 50 normal non-pregnant women of similar age were studied as a control. The findings are shown in Tables I, II and III.

(*a*) *Incidence of Frequency*

Study of the habits of women in the control series (Table I) shows that the normal young non-pregnant adult usually empties the bladder 4 to 6 times during the 24 hours. Very few such women ever void during the night, and then only occasionally. These findings are generally in

TABLE I

Voiding Habit of Normal Non-Pregnant Women

No. of Diurnal Voiding Acts	No. of Women	No. of Nocturnal Voiding Acts	No. of Women
Less than 3	—	None	45
3	2	1 (occasionally)	4
4	13	1 (regularly)	1
5	20	More than 1	—
6	15		
More than 6	—		
	50		50

agreement with those of Campbell (1957). The occurrence of frequency during pregnancy was only accepted when a woman noticed a gross and constant deviation from her pre-pregnancy habit. This meant that the average number of voiding acts rose to 7 or more by day and to 1 or more by night. By this standard, frequency of micturition was noted at some stage of pregnancy by 324 out of 400 women (81 per cent). The incidence was the same for both primigravidae and multigravidae (Table II).

(*b*) *Timing of Frequency in Relation to Night and Day*

Only 50 of the pregnant women suffering from frequency reported that the symptom was present only during the day time. All the remaining 274 (84 per cent) were troubled by night as well as by day. In this large majority the frequency was not obviously related to sleep, posture and activity.

TABLE II

Incidence of Frequency in Pregnancy
Percentages in Brackets

	Number	Frequency Present	Frequency not Present
Primigravidae ..	222	180 (80)	42
Multigravidae ..	178	144 (82)	34
	400	324 (81)	76

(*c*) *Relationship of Frequency to the Period of Pregnancy*

The commonest time of onset for the bladder disturbance was the first trimester, frequency being noted at this time by 238 women. In all except 14 of these, the symptom became progressively worse throughout pregnancy, reaching a maximum in the last month. The exceptions experienced some relief during mid-pregnancy. Twenty women found that frequency only started in mid-pregnancy and then became gradually worse up to term. The remaining 66 noted frequency in the later weeks only. The conclusion is that frequency, when it occurs, is nearly always a progressive symptom, usually starting early in pregnancy but occasionally at later stages; once present it generally becomes increasingly worse until term. The classical concept of frequency occurring early in pregnancy, disappearing in mid-pregnancy and returning in the later weeks, is without statistical support.

TABLE III

Occurrence of Frequency

Early Pregnancy	Mid-Pregnancy	Late Pregnancy
238	224*	238†
	20	20†
		66
238	244	324

* Frequency improved in mid-pregnancy in 14 cases.
† Frequency always worst in last month of pregnancy.

(2) THE CAUSE OF FREQUENCY

Various explanations of urinary frequency during pregnancy have been put forward.

(*a*) *Position of the Uterus*

Croom (1884) suggested that frequency in the first 3 months of pregnancy is caused by retroversion of the uterus. He considered that traction exerted by the utero-vesical ligaments prevents the bladder from expanding and went so far as to say that the occurrence of frequency is diagnostic of uterine retro-displacement. The observations recorded here, however, suggest that this

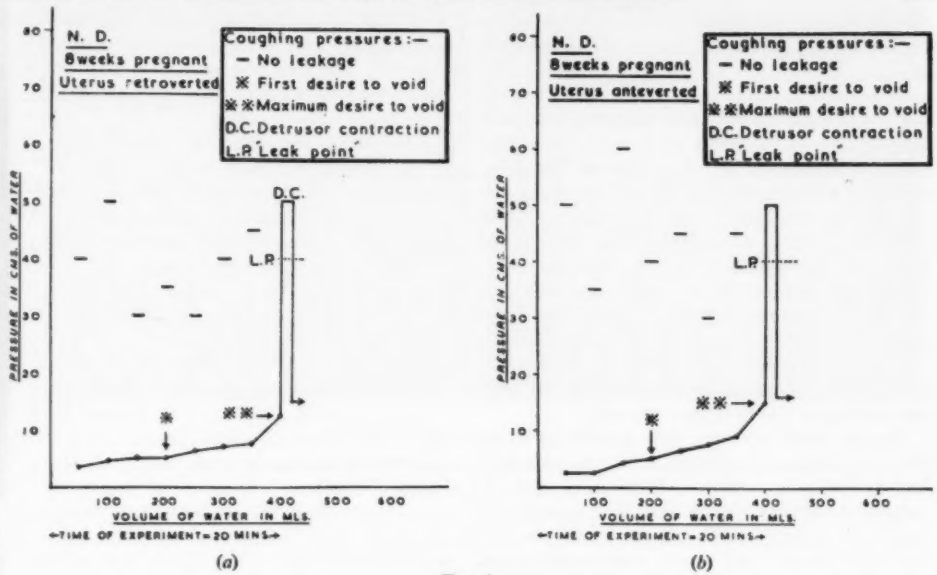


FIG. 1

Cystometry in a multigravid patient before and after correction of a retroverted gravid uterus. The main features are identical. The bladder capacity and intravesical pressure are the same as in the normal non-pregnant woman.

bladder symptom occurs even in the absence of retroversion; moreover, it persists until mid-pregnancy and later, when any uterine retrodisplacement has disappeared.

Only 25 of the women with frequency in the early weeks of pregnancy had a retroverted uterus; these were all subjected to cystometry. None showed any evidence of reduced bladder capacity or of heightened bladder tone and pressure. In each case the position of the uterus was corrected and maintained by means of a Hodge pessary, cystometry being repeated one week later. The second cystometrograph was always similar to the first (Fig. 1).

Cystograms of 9 women in the early weeks of pregnancy (not included in the series under review) were also available for study. Four of these consisted of the penultimate exposure at intravenous pyelography; these were obtained 6 years previously when the possible dangers of radiation hazards to the mother and foetus were not fully appreciated. The remaining 5 radiographs were the result of planned urethrocystography in women destined to have therapeutic abortion and tubal ligation performed on medical grounds. In 2 of the latter cases X-ray exposures were made with the uterus in both anteversion and retroversion (Fig. 2) and they clearly show that uterine position does not affect the contour of the bladder base and urethro-vesical junction as postulated by Croom (1884).

The conclusion is that retroversion does not cause any bladder symptoms during pregnancy unless the uterus becomes impacted in the pelvis to produce retention.

(*b*) *Mechanical Pressure on the Bladder*

It is stated in most textbooks that frequency in the first trimester is the result of the heavy, sharply anteflexed uterus pressing on and irritating the bladder. Similarly, in late pregnancy, descent of the presenting part of the foetus is alleged to irritate the bladder. Indeed,

the onset of frequency in late pregnancy is commonly said to be a symptom of engagement of the head.

The shape of the fundus of the bladder is certainly distorted by the early pregnant uterus, as can be seen in the series of 9 cystograms mentioned above (Fig. 3). Also, during late pregnancy, the presenting part presses on the top of the bladder tending to make it take an hour-glass shape. This is evident in the illustrations published by Schubert (1929), Malpas *et al.* (1949) and Kantor *et al.* (1949) and was confirmed by the writer who, in 50 patients who had to have lateral pelvimetry in the later weeks of pregnancy for obstetric reasons, carried out simultaneous urethrocystography (Fig. 4) without adding to the radiation hazards.

Despite these findings, and despite its superficial attraction, it is difficult to accept a mechanical basis for frequency. If there were such, the urinary symptoms should vary with posture and would be expected to be present by day and not by night. As reported above, such variations do not occur and this fact alone goes far to disprove the theory so far as early pregnancy is concerned. If further proof be needed, it is provided by cystometric studies which, as described later, show no evidence of reduced bladder capacity or tolerance in early pregnancy. At that time any reduction in the supero-inferior dimension of the bladder is compensated by lateral expansion (Fig. 3). In late pregnancy it may be argued that the foetal presenting part exerts pressure even when the woman is lying down. This, together with the fact that there is evidence of reduced bladder capacity in the third trimester, makes it impossible to exclude mechanical pressure as at least one factor causing frequency in the weeks immediately preceding term. At other times, however, the size and weight of the pregnant uterus play no part in producing the symptom.

(*c*) *Increased Irritability of the Bladder Wall Leading to Reduced Bladder Capacity*

It is not unreasonable to suppose that the bladder muscle might become more irritable in pregnancy. Such irritability could be caused by:

(i) Hyperaemia of the trigone.

(ii) Increased tone of the detrusor muscle secondary to changes in the nervous or hormonal control.

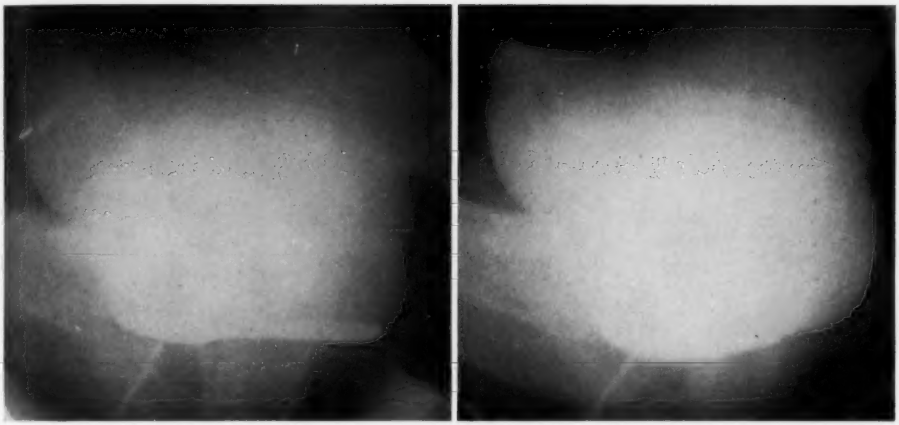
Theories to this effect were put forward, mainly as a result of theoretical considerations alone, by Crabtree (1942), Shaw (1949), Greenhill (1955) and others. In order to test them, 150 of the 400 patients under study were subjected to cystometry. The three trimesters of pregnancy were covered, there being 50 women in each group. Some of these had frequency, others did not; their selection depended only on their willingness to co-operate. The method used for cystometry was that described by Roberts (1951) and the findings were as follows:

(i) *The First Trimester.* During the first 3 months of pregnancy the average bladder capacity was 410 ml. This is the same as for normal non-pregnant women (Muellner, 1939; Langworthy *et al.*, 1940; Roberts, 1951; and Campbell, 1957). It also tallies with the findings of Crabtree (1942) who noted no change in the bladder capacity of women suffering from urinary frequency in early pregnancy. The volume of fluid tolerated showed wide individual variations (Table IV) but generally there was no

TABLE IV

Cystometry in First Trimester of Pregnancy. Average Bladder Capacity, 410 ml.

Bladder Capacity ml.	Frequency Present	Frequency Absent	Total
Less than 100 ..	2 patients	–	2
100–300	6 patients	–	6
300–500	18 patients	8 patients	26
500–700	8 patients	2 patients	10
700–900	4 patients	–	4
900–1,100	—	2 patients	2
Total	38	12	50



(*a*) (*b*)

FIG. 2

Lateral urethrocystography in a normal multiparous woman, 10 weeks pregnant, at rest.

(*a*) Uterus retroverted.

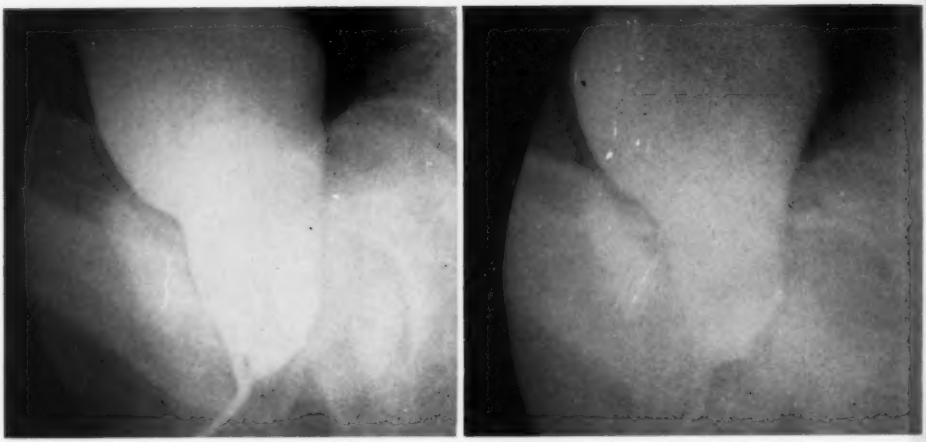
(*b*) Uterus anteverted and held in place with a Hodge pessary. The position of the urethra and the bladder base, as well as the shape of the urethro-vesical junction are not affected by the uterine position. They are the same as in the normal non-pregnant patient.

FIG. 3

Antero-posterior cystogram obtained as part of intravenous pyelography series of radiographs. Primigravida, 14 weeks pregnant, uterus anteverted. The distortion of the bladder by the enlarged uterus is typical of the stage of pregnancy. Reduction in supero-inferior diameter is compensated by lateral expansion of the bladder.

FIG. 4

Lateral urethrocystography carried out simultaneously with lateral pelvimetry. Normal primigravida at term. The presenting part distorts the fundus of the bladder giving it an hour-glass shape. In this case the posterior urethro-vesical angle is poor; this is because the patient suffered stress incontinence of pregnancy.



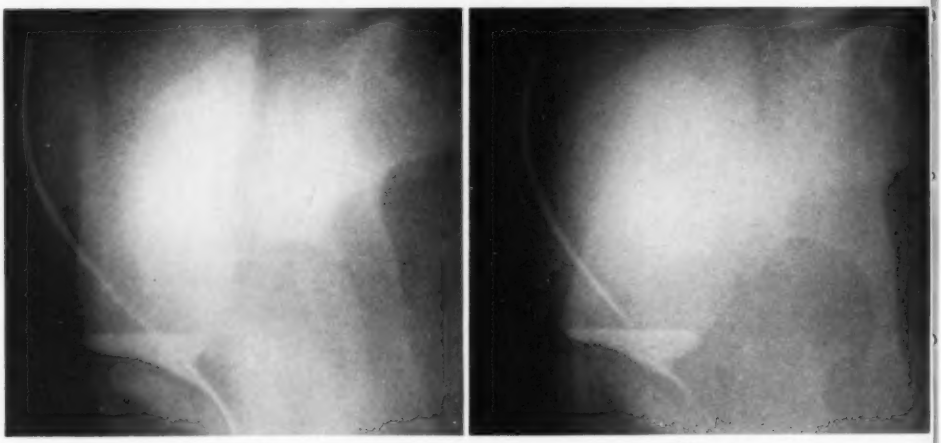
(*a*) (*b*)

FIG. 6

Lateral urethrocystography in a gravida-2, 11 weeks pregnant with twins (Case 1). Uterus retroverted and impacted and patient suffering from urinary retention.

(*a*) Patient resting easily, urethra marked by soft rubber catheter. There is no elevation of the urethro-vesical junction which lies at the lower border of the symphysis pubis.

(*b*) Catheter removed, patient attempting to void but only passing a small stream down urethra. The posterior urethro-vesical angle persists.



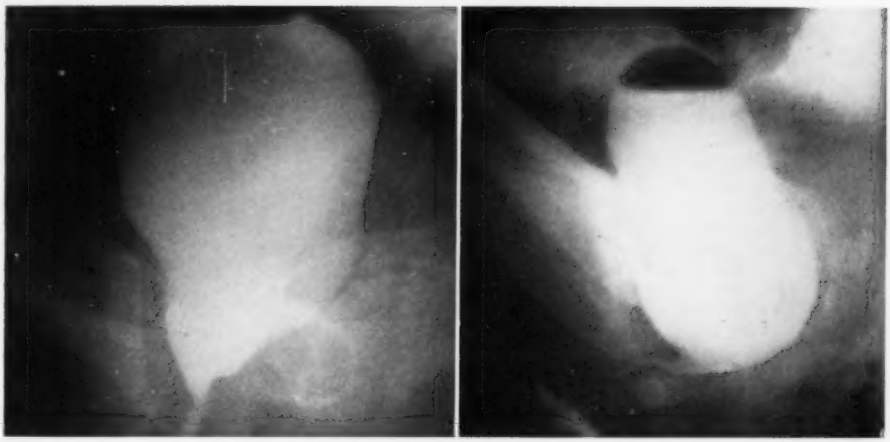
(*a*) (*b*)

FIG. 7

Lateral urethrocystography in a gravida-1, 13 weeks pregnant. Impacted retroverted gravid uterus and patient suffering urinary retention (Case 2).

(*a*) Patient resting easily, urethra marked by a soft rubber catheter. There is no urethral elongation, the urethro-vesical junction lying behind the mid-point of the symphysis pubis.

(*b*) Patient attempting to void with the catheter still in place. The posterior urethro-vesical angle persists.



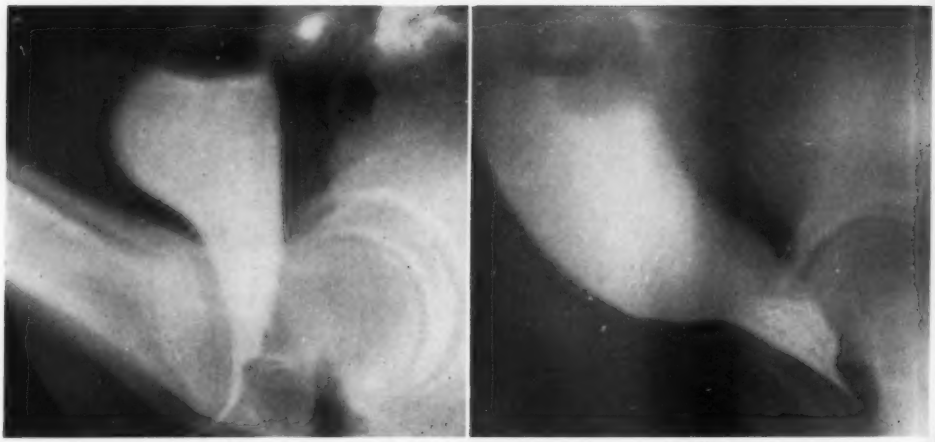
(*a*) (*b*)

FIG. 9

Lateral urethrocystography in a gravida-3, 14 weeks pregnant. This patient suffered acute retention of urine due to impaction of a retroverted gravid uterus (Case 4).

(*a*) The catheter is outlining the urethra. The uterus is retroverted and the patient is unable to void. The bladder is ovoid in shape but the posterior urethro-vesical angle persists. The urethro-vesical junction is not elevated: it lies behind the lower part of the symphysis pubis.

(*b*) The catheter has been removed, the uterus is anteverted and kept in position by a Hodge pessary. The patient is now voiding normally. Detrusor contraction is occurring as evidenced by crenations in the posterior bladder wall, and the posterior urethro-vesical angle has disappeared.



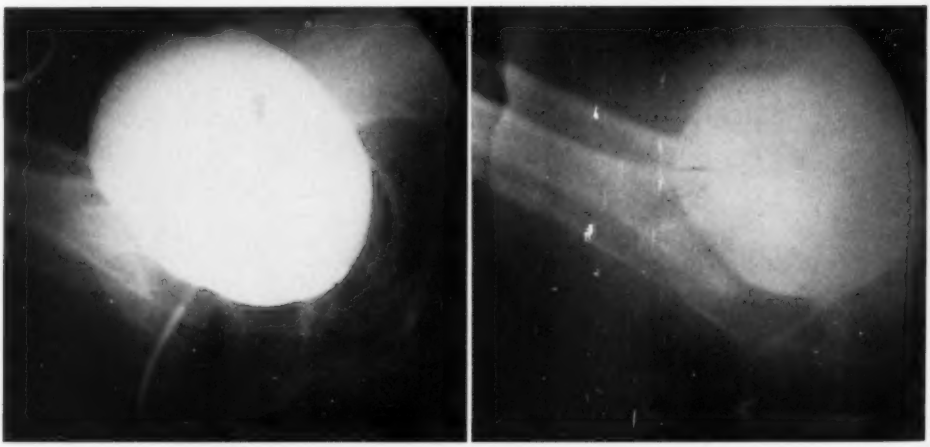
(*a*) (*b*)

FIG. 10

Lateral urethrocystography in 2 cases of urinary retention due to impacted fibroids. Both were attempting to void at the time of radiography and each succeeded in passing only a small amount of urine into the urethra. This allows the urethra to be seen in the illustrations. In each case it is to be noted that the urethro-vesical junction is not elevated and the urethra is not elongated. The striking feature is the persistence of the posterior urethro-vesical angle despite contraction of the bladder detrusor.

(*a*) E.H. Aged 50 years. Multiple fibroids subsequently treated by hysterectomy.

(*b*) M.T. Aged 47 years. Single cervical fibroid subsequently treated by hysterectomy.



(*a*) (*b*)

FIG. 11

Lateral urethrocystographs of a multiparous patient, aged 35 years, with a tight gauze pack in the vagina 18 hours after cervical biopsy.

(*a*) The pack is in the vagina and the patient is unable to void. The position of the urethra is therefore indicated by a soft catheter. The urethro-vesical junction lies in the normal position behind the symphysis pubis. The posterior urethro-vesical angle persists during attempted voiding and despite contraction of the bladder wall.

(*b*) The pack has been removed from the vagina and voiding is occurring. The posterior urethro-vesical angle has disappeared, the bladder base and urethra lying in a straight line.

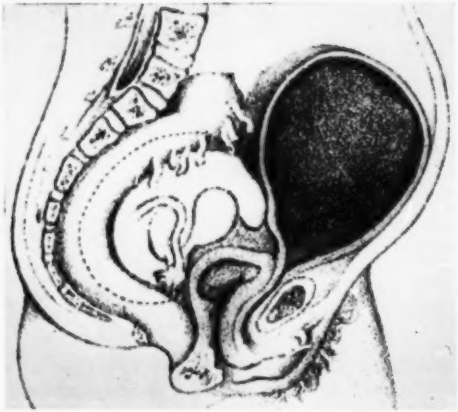


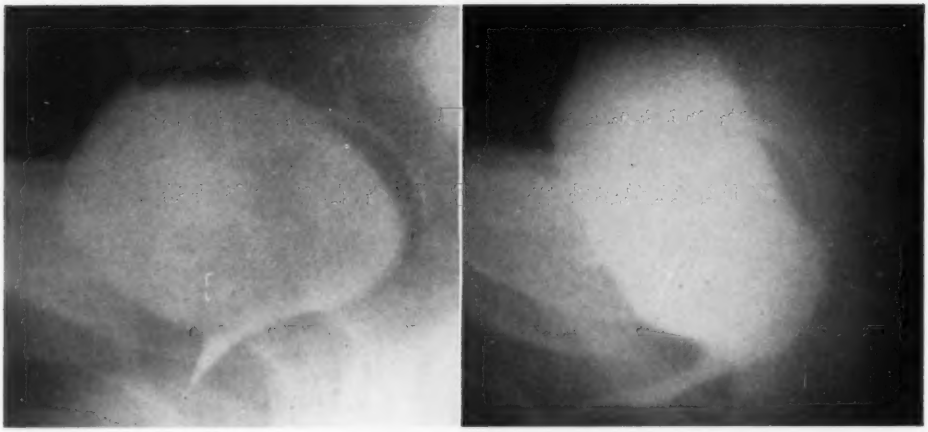
FIG. 12a

Frozen section of the pelvis of a woman dying as a result of acute retention of urine due to impaction of a retroverted gravid uterus (F. Schatz, 1870, *Arch. Gynäk.*, **1**, 469). The appearances at first suggest that the urethra is not elongated but they are deceptive. What appears to be the upper urethra is the collapsed lower part of the bladder as was pointed out by Schatz in his original description. He noted that the urethro-vesical junction is in its normal position.

Key: A=body of uterus.
B=vagina.
C=cervix.
D=urethra.
E=bladder.

FIG. 12b

Frozen section of the bladder and uterus of a woman dying as a result of acute retention of urine due to impaction of a retroverted gravid uterus. The depression on the front of the bladder indicates the position of the symphysis pubis. It will be noted that the urethro-vesical junction is below the lower part of this. The urethra is neither compressed nor elongated. This is emphasized in the text by Croom. (Reproduced from *Retroversion and Retroflexion of the Gravid Uterus*, by J. H. Croom, Edinburgh, 1890. Oliver and Boyd.)



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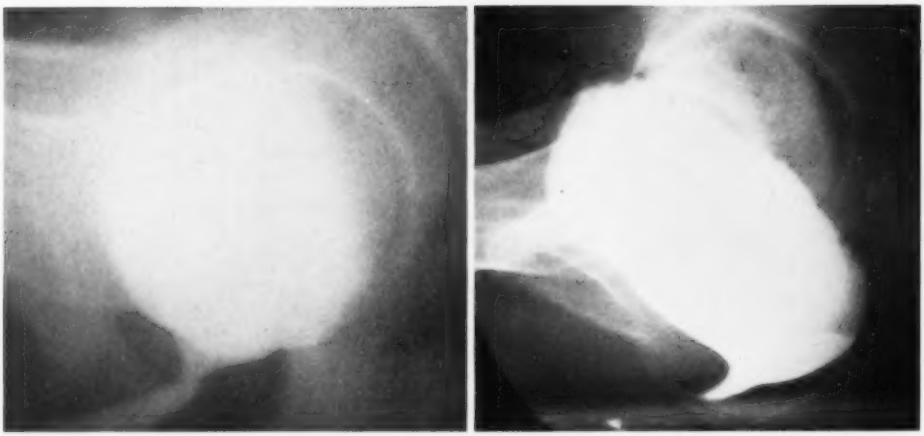

(*c*) (*d*)

FIG. 13

Lateral urethrocystography in the normal, non-pregnant nulliparous woman.

(*a*) Early micturition. The bladder is ovoid in outline, medium is entering the urethra and the bladder base and urethra lie in a straight line.

(*b*) Micturition established. The bladder is ovoid in outline, detrusor contraction is present as evidenced by crenations in the posterior bladder wall. The urethra and bladder base lie in a straight line.

(*c*) Late micturition. Detrusor contraction is still present, but the posterior urethro-vesical angle is returning.

(*d*) Voluntary arrest of micturition. After voiding some of the medium the subject is asked to stop the act and this results in the urethral stream being arrested at the level of the urogenital diaphragm and presumably by the external sphincter. The arrest occurs despite continued detrusor contraction.

FIG. 14

Lateral urethrocystography in a case of urinary retention 24 hours after delivery. Primipara, aged 20 years, delivered by forceps with episiotomy. The shape of the bladder indicates that the detrusor is contracting and this has resulted in opening of the upper urethra with obliteration of the posterior urethro-vesical angle. The stream is arrested at the level of the external urethral sphincter, presumably because of spasm of this muscle. Compare with Figure 13 (*d*).

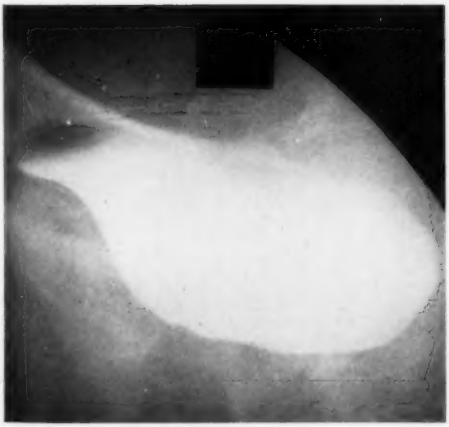

FIG. 15

Lateral urethrocystography in a case of urinary retention 24 hours after lower segment Caesarean section. Primipara, aged 35 years. The patient is attempting to void but the bladder remains inert. No medium is therefore visible in the urethra.

FIG. 16

Lateral urethrocystography in a case of urinary retention 48 hours after a Manchester operation for prolapse. A.D., aged 47 years. The patient is attempting to void and the shape of the bladder indicates that the detrusor muscle is active. This is opening the upper urethra with obliteration of the posterior urethro-vesical angle. The stream of medium is arrested at the level of the urogenital diaphragm, presumably from spasm of the external urethral sphincter. Note the similarity to Figure 14.

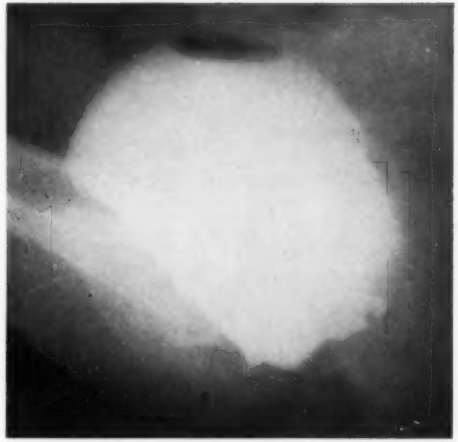

FIG. 17

Lateral urethrocystography in a case of urinary retention 6 days after urethroplasty for stress incontinence of urine. F.E., aged 50 years, attempting to void. Bladder base still shows some distortion from anterior colporrhaphy and the inter-ureteric bar is seen as a filling defect. The bladder is contracting and the urethral meatus has opened slightly, but the posterior urethro-vesical angle persists. Although some spasm of the external sphincter cannot be excluded the main difficulty in this case appears to be a failure to obliterate the posterior urethro-vesical angle, probably because of suturing at that site. There is temporary over-correction of the angle.

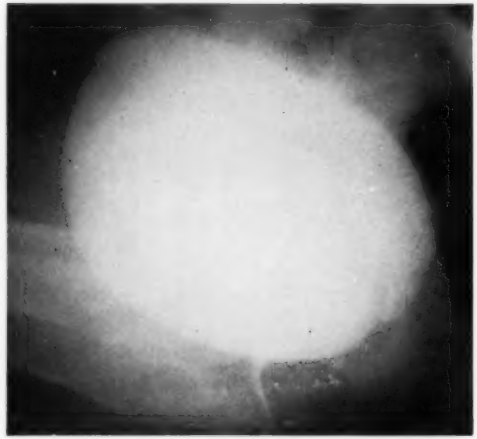

FIG. 18

Lateral urethrocystography in a case of urinary retention 1 month after a urethral sling operation. A.S., aged 48 years, attempting to void. The bladder is contracting and the patient has succeeded in getting a small stream into the urethra. The posterior urethro-vesical angle persists and this is the main difficulty. In this case the angle was over-corrected by making the sling too tight.

TABLE V

Cystometry in Second Trimester of Pregnancy. Average Bladder Capacity, 460 ml.

Bladder Capacity ml.	Frequency Present	Frequency Absent	Total
Less than 100 ..	—	–	—
100–300	9 patients	1 patient	10
300–500	14 patients	2 patients	16
500–700	11 patients	9 patients	20
700–900	3 patients	1 patient	4
900–1,100	—	–	—
Total	37	13	50

correlation between the volume which could be held with comfort and the presence or absence of frequency. Those women (8 in all) who had a capacity of less than 300 ml. of fluid all suffered frequency and urgency but, on enquiry, it was found all had had similar symptoms prior to pregnancy. They had, in fact, a long-standing unusual voiding habit.

(ii) *The Second Trimester.* In mid-pregnancy, again, the average bladder capacity (460 ml.) was not reduced and the intra-vesical pressure was not raised above normal. Out of 10 women with a capacity of less than 300 ml. all except one noted frequency. However, many women with a normal or large bladder tolerance also suffered to the same extent (Table V).

(iii) *The Third Trimester.* In late pregnancy there is evidence of reduced bladder capacity, and correspondingly increased detrusor irritability (Fig. 5). Only 3 women could tolerate more than 500 ml. and none of these had frequency. Twenty-five out of the 50 women (50 per cent) had a capacity of less than 300 ml. and the average capacity was only 272 ml. (Table VI). This finding is not in agreement with that reported by Muellner (1939) who found that the bladder capacity increased up to 1,300 ml. in the 8th month and remained at that level until term. Youssef (1956), in a small series of cases, found a similar increase in capacity up to 2 weeks before term when a reduction occurred in relation to the engagement of the foetal head.

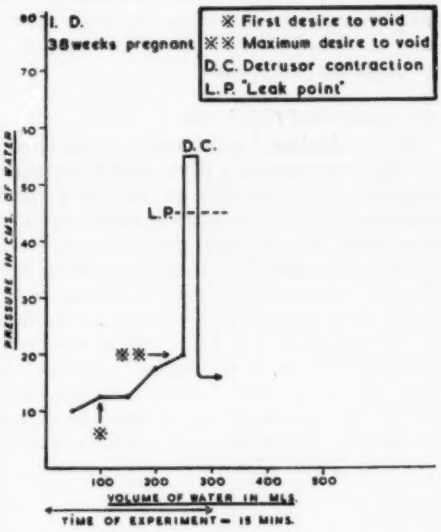

FIG. 5

Cystometrogram. Primigravida, 38 weeks pregnant. Bladder capacity reduced, intravesical pressure rising when fluid content exceeds 150 ml. and inhibition of the detrusor failing at 250 ml. This change in bladder function is not uncommon in the later weeks of pregnancy but is absent before this time.

Increased irritability and decreased capacity of bladder in late pregnancy, as found in this investigation, might be determined by crowding of the pelvic viscera by the presenting part but

TABLE VI

Cystometry in the Third Trimester of Pregnancy. Average Bladder Capacity, 272 ml.

Bladder Capacity ml.	Frequency Present	Frequency Absent	Total
Less than 100 ..	6 patients	–	6
100–300	18 patients	1 patient	19
300–500	14 patients	8 patients	22
500–700	—	3 patients	3
700–900	—	–	—
900–1,100	—	–	—
Total	38	12	50

could be explained on the basis of increased muscle tone, brought about possibly by hormonal or nervous influences. The latter view is more in accord with the fact that frequency is not dependent on posture.

(*d*) *Polyuria and Polydypsia*

Having eliminated other explanations, at least for frequency occurring in the first 6 months of pregnancy, it is necessary to consider a simple causal mechanism such as an increased output of urine. With this in mind, the 150 women subjected to cystometry, 50 in each trimester, were asked to measure their urinary output over a period of 24 hours. The average daily excretion of these patients was 1,917 ml. in the first 3 months, 2,020 ml. in the second 3 months, and 1,820 ml. in the third 3 months of pregnancy. All of these figures are higher than the average recorded in 50 non-pregnant controls, namely, 1,475 ml. (Table VII).

It was therefore decided to measure the fluid intake as well as the urinary output of 100 of the total 400 normal pregnant women. They were selected according to their intelligence and willingness to co-operate. Forty were in the first trimester of pregnancy and 30 in each of the other trimesters. Each kept a record of her 24-hourly intake of fluid and output of urine during a continuous period of 72 hours. Twenty of these patients were able to make these observations on 3 separate occasions in each trimester of their pregnancies. The findings were compared with those of a control series of 50 non-pregnant patients in the same age group and are shown in Tables VIII and IX.

The average daily output in this series of pregnant women was 1,895 ml. in the first trimester, 2,021 ml. in the second trimester and 1,765 ml. in the third. These figures are very similar to those obtained for the first group (Table VII), a consistency which goes to indi-

TABLE VII

Urinary Output ml.	Number of Pregnant Women				Number of Non-Pregnant Women
	First Trimester	Second Trimester	Third Trimester	Total	
Less than 500 ..	—	—	—	—	—
500–1,000	—	—	—	—	5
1,000–1,500	6	4	7	17	26
1,500–2,000	24	19	27	70	16
2,000–2,500	20	27	16	63	3
Average output ..	1,917 ml.	2,020 ml.	1,820 ml.	1,919 ml.	1,475 ml.

TABLE VIII

Average Daily Fluid Intake and Urinary Output

No. of Women	Pregnant Women						Non-Pregnant Women	
	First Trimester		Second Trimester		Third Trimester			
	Intake ml.	Output ml.	Intake ml.	Output ml.	Intake ml.	Output ml.	Intake ml.	Output ml.
40	1,993	1,895						
30			2,065	2,021				
30					1,904	1,765		
50							1,434	1,475

TABLE IX

Average Daily Intake and Average Daily Urinary Output of 20 Women Observed Throughout Pregnancy

Name	Average Daily Fluid Intake			Average Daily Urinary Output		
	First Trimester ml.	Second Trimester ml.	Third Trimester ml.	First Trimester ml.	Second Trimester ml.	Third Trimester ml.
D.A.	1,080	1,180	1,080	1,080	1,200	1,080
M.M.	820	820	820	1,080	980	800
M.C.	2,700	2,700	2,500	2,160	3,060	2,700
D.S.	2,430	2,520	2,000	1,890	2,260	1,980
M.B.	1,890	1,980	1,700	1,404	2,250	1,800
D.D.	1,880	1,790	1,600	1,630	1,900	1,550
A.D.	2,650	2,650	2,580	2,250	2,250	2,000
C.B.	1,850	1,980	1,850	1,550	1,680	1,550
M.E.	1,600	1,400	1,980	1,790	1,120	1,920
J.E.	2,650	2,760	2,400	2,300	2,500	2,000
J.F.	1,850	1,980	1,760	1,350	1,800	1,400
H.D.	1,620	1,620	2,620	1,230	1,260	2,220
M.J.	1,980	1,990	1,890	1,700	2,010	1,670
O.G.	2,020	2,300	2,100	1,990	2,560	1,800
E.H.	1,890	1,980	1,780	1,500	1,860	1,690
T.J.	2,385	2,400	2,350	2,300	2,560	2,300
L.A.	2,700	2,700	2,400	2,400	3,000	1,980
J.D.	1,990	2,100	1,880	2,170	2,060	1,700
G.T.	2,250	2,360	1,980	1,950	2,210	1,760
M.F.	1,890	1,980	1,690	2,100	2,080	1,600

cate reliability. The average fluid intake was 1,993 ml. in the first trimester, 2,065 ml. in the second trimester and 1,904 ml. in the third trimester, as compared with 1,434 ml. in the non-pregnant women.

The frequency of pregnancy would therefore seem to be explained by polyuria, an explanation which readily accounts for both nocturnal and diurnal frequency. This polyuria is associated with an increased intake of fluid but it remains to be shown which is the cause and which the effect. A change in hypothalamic function in pregnancy might account for increased ingestion of fluid and therefore polyuria. On the other hand, it is known that glomerular filtration is increased 50 per cent during pregnancy (Bücht and Werkö, 1953) and, unless the renal tubules re-absorb most of the resulting fluid, its excretion

must stimulate the woman to drink more. One or other of these mechanisms probably explains why thirst is a common reaction to pregnancy.

Retention of Urine

(1) During Pregnancy

Urinary retention is not commonly encountered during pregnancy. Apart from the possibility of its being a manifestation of organic or functional disease of the central nervous system, it is classically caused by impaction of the retroverted gravid uterus, or of a tumour, in the pelvis. Its occurrence at the 12th to 14th week of pregnancy in a retroverted uterus was described by Smellie (1754), and studied in some detail by Croom (1890). More recent workers on this subject include Burdon *et al.* (1951), Seidner *et al.* (1952), Spring and Hynes (1952), Ney and Hyman (1954), Badenoch (1955), Studdy (1955) and Devoe (1956). Impaction of the retroverted gravid uterus with acute retention of urine appears to be decreasing in incidence, possibly because of the gradual disappearance of the pelvis whose sacral promontory projects forward to obstruct the rising fundus of the uterus. Nevertheless, the syndrome is still encountered and therefore receives attention in all textbooks.

The usual explanation of the difficulty in micturition is that the uterus, by filling the pelvis, displaces the bladder into the lower abdomen thus stretching and narrowing the urethra. The upward movement of the cervix and of the lower part of the anterior uterine wall, to which the bladder is attached, may also, it is said, play a part in lifting the urethro-vesical junction. Since there is no difficulty in passing a catheter in these cases it is generally accepted that the retention is not caused by the pelvic tumour exerting direct pressure on the urethra. It is variously attributed to:

(i) Attenuation of the urethra (Berkeley, 1941; Shaw, 1949; Gibberd *et al.*, 1956; Brews, 1957; Johnstone and Kellar, 1957).

(ii) Increased resistance of the urethra to dilatation (Brews, 1957).

(iii) An unspecified reflex disturbance of the neuromuscular mechanism of micturition (Berkeley, 1941; Gibberd *et al.*, 1956; Johnstone and Kellar, 1957).

Fundamental to all these theories, however, is the concept that the bladder base is lifted and the urethra elongated.

Six years ago, before radiation risks were appreciated, urethrocystography was carried out on two women at a time when they suffered urinary retention as a result of impaction of a retroverted gravid uterus. The radiographs were fortunately preserved and became available for study as Cases 1 and 2. The technique employed was that described by Roberts (1951, 1952, 1953) and Jeffcoate and Roberts (1952a, b, 1954), the bladder and urethra being made radio-opaque by the instillation of 120 ml. of 12·5 per cent sodium iodide and 15 ml. "Neohydriol". Radiographs were taken with the patients resting and attempting to void (Figs. 6 and 7). They showed that the situation was not as might be expected. The main findings in both cases were:

(*a*) *With the Patient Resting and a Soft Catheter in the Urethra*

(i) The urethra was not elongated.

(ii) The urethro-vesical junction, although displaced forwards behind the symphysis pubis, was no higher in the pelvis than it is in the normal non-pregnant woman.

(iii) The anterior urethro-vesical angle had disappeared, possibly as a result of pressure against the symphysis pubis. The posterior urethro-vesical angle persisted although the arm made by the trigone appeared rather short.

(*b*) *During Attempts to Void*

(i) Only one of the two patients succeeded in forcing a few drops of fluid from the bladder into the urethra. In this, and in the second case the posterior urethro-vesical angle persisted.

(ii) Disappearance of the posterior angle with the opening of the urethra from above downwards, which is characteristic of the initial stages of normal voiding (Roberts, 1951, 1953; Jeffcoate and Roberts, 1952a, b, 1956; Jeffcoate, 1957, 1958), did not take place, despite contraction of the detrusor muscle of the bladder.

(iii) The urethro-vesical junction was not lifted in the pelvis.

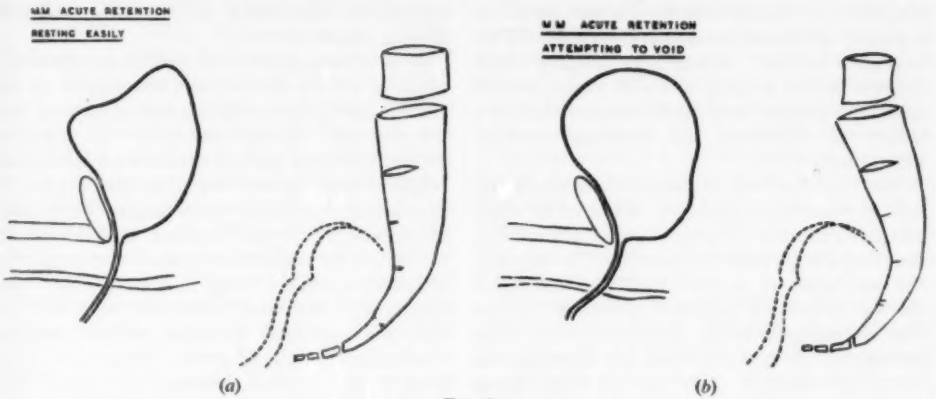

FIG. 8

Tracings of lateral urethrocystographs obtained from a gravida-6, 14 weeks pregnant. This patient suffered acute retention of urine due to impaction of a retroverted gravid uterus (Case 3).

(*a*) The patient is resting easily. The urethra is marked with a soft rubber catheter. There is no elevation of the urethro-vesical junction which lies behind the lower part of the symphysis pubis.

(*b*) The patient is attempting to void with the catheter still in the urethra. The posterior urethro-vesical angle persists.

These findings appeared so important that search was made for further cases which could be studied radiologically without risk. Only 3 opportunities occurred within the last 3 years. The first patient (Case 3), a widow aged 42 years, already had signs of inevitable abortion. The second patient (Case 4) was also in process of aborting; she, moreover, had a Rhesus negative blood group, Rhesus antibodies in the blood and a husband whose blood group was Rhesus positive (homozygous). The last patient (Case 5) had had 9 previous pregnancies with 8 living children and was also suffering from inevitable abortion. All these women had acute retention of urine caused by impaction of a retroverted uterus and none proposed to have further pregnancies.

At the time of urethrocystography none of the patients was able to void. The radiographs show the same appearances as those obtained in the first two cases (Fig. 8). The urethro-vesical junction is at a normal level, the urethra is not elongated, and the posterior urethro-vesical angle persists during attempts to void. In Case 4 urethrocystography was carried out both before and after correction of the position of the uterus, and the difference between the radiographs is striking. Before replacement of the uterus the patient failed to open the internal meatus but as soon as the uterus was in normal position she was able to put in motion the normal voiding mechanism; the posterior urethro-vesical angle disappeared and the urethra opened from above downwards (Fig. 9).

To test the conclusion that retention of urine in these cases is caused by interference with the obliteration of the posterior urethro-vesical angle and not by an uplift of the urethro-vesical junction and attenuation of urethra, urethrocystography was next carried out on 8 non-pregnant women suffering from pelvic tumours which caused difficulty or inability to void. These patients were post-menopausal or destined for hysterectomy so their investigation did not involve radiation hazards to potential offspring.

The radiological appearances of the bladder and urethra in these cases (Fig. 10) are identical with those which are found when urinary retention is caused by impaction of a retroverted gravid uterus. The urethra is not elongated, even

when clinical examination reveals that the cervix is grossly displaced upwards and forwards by the impacted tumour. Attempts at voiding which either failed or resulted in a tiny trickle of fluid down the urethra were again characterized by a failure to obliterate the posterior urethro-vesical angle.

The final test was to induce deliberately this type of retention of urine by means of an artificial pelvic tumour. This was done in 4 women by inserting a large pack of gauze into the vagina at the conclusion of an operation which involved cervical biopsy for suspected carcinoma *in situ*. The radiographs taken 18 hours later, when urinary retention was present, are identical with those obtained in cases of impacted pelvic tumour. Moreover, removal of the pack resulted immediately in restoration of the patient's ability to open the upper urethra—as demonstrated both radiologically and clinically (Fig. 11). All the evidence therefore shows that retention associated with impaction of a retroverted gravid uterus or of any pelvic tumour, is not caused by an uplift of the bladder into the abdomen and by stretching and narrowing of the urethra. It is the result of the pelvic tumour interfering with the normal mechanism whereby the internal urethral meatus opens. The disturbance is one which involves the posterior aspect of the urethro-vesical junction but it is impossible to say whether the failure to obliterate the posterior urethro-vesical angle reflects a crowding of all the pelvic organs or whether it is a result of displacement of the cervix and anterior vaginal wall.

Since the traditional explanation of retention in these cases is not true, it is natural to wonder how it arose. The history is similar to that of so many fallacies in medicine. Schatz (1870) and Croom (1890) each studied frozen sections of the pelvis of women dying from unrelieved impaction of the uterus. They described and illustrated their findings in detail (Fig. 12a and b). In so doing each emphasized that the urethra was neither compressed nor elongated. Unfortunately, those who subsequently purported to quote this work misinterpreted the illustrations and, without reference to the original text, propagated the false idea that the bladder base is lifted and the urethra stretched. This was then copied by one writer from another without serious question.

It is of interest to note that views about the position of the bladder and the length of the urethra during labour have a similar history. For the first half of this century it was generally believed that the bladder becomes an abdominal organ during labour and that the urethra is lengthened. This belief arose despite the findings of Braune (1872) and Barbour (1889) who, at the end of the nineteenth century, studied frozen sections of women dying in labour. They concluded that the urethra is *not* lengthened and that the urethro-vesical junction always remains behind the symphysis pubis. Those who wrote later, however, were deceived by a superficial examination of the original illustrations and neglected the legends to found and to spread an erroneous concept. This persisted until Malpas *et al.* (1949) and Kantor *et al.* (1949) confirmed the original anatomical findings by urethro-cystography carried out on women in labour.

(2) In the Puerperium

The most common time for retention to occur in relation to child-bearing is in the puerperium. It is variously attributed to:

(i) Nervousness, modesty and similar factors causing inhibition by the central nervous system (Berkeley, 1941).

(ii) An unnatural posture (Berkeley, 1941; Shaw, 1949; Greenhill, 1955; Studdy, 1955).

(iii) Lack of elasticity of the bladder (Greenhill, 1955).

(iv) Injury, swelling and bruising of the vulva, urethra and bladder trigone (Berkeley, 1941; Greenhill, 1955; Studdy, 1955).

(v) Reflex spasm of the external urethral sphincter from tears and incisions in the perineum (Berkeley, 1941; Greenhill, 1955; Studdy, 1955).

(vi) An unspecified temporary derangement of the neuromuscular mechanism of the bladder and urethra (Shaw, 1949).

To appreciate what may be happening it is necessary to refer back to the process of micturition in the normal woman. Present-day views on this derive mainly from the work of Langworthy *et al.* (1940), Muellner and Fleischner (1949),

Muellner (1951, 1958), Roberts (1953), Hinman *et al.* (1954, 1955), Benjamin *et al.* (1955), Ardran *et al.* (1956a, b), Langreder (1956), Lund *et al.* (1957), and Caine and Edwards (1958). They suggest that voiding is initiated by the woman contracting the abdominal muscles and relaxing the levatores ani. As a result the bladder base and the upper urethra are allowed to move downwards, rotating round a fixed point at the urogenital diaphragm (triangular ligament). The detrusor muscle of the bladder, voluntarily released from central inhibition, then contracts and dilatation of the urethra occurs from above downwards (Fig. 13a). The opening of the upper urethra, brought about by contraction of the bladder detrusor muscle, is associated with the disappearance of what appears on silhouette in lateral radiographs as a "posterior urethro-vesical angle", the trigone and floor of the urethra coming into line (Fig. 13b). Although the posterior angle tends to be partly restored towards the end of micturition (Fig. 13c) or when voiding is hesitant through nervousness, its obliteration is essential to the initiation of the outflow.

The above process can be inhibited or arrested voluntarily by the woman. She does this by contracting the voluntary external urethral sphincter (compressor urethrae) at the level of the urogenital diaphragm. The stream is cut off at this point (Fig. 13d) and the urethra then closes from below upwards, any fluid being returned to the bladder.

Consideration of these matters permits the postulation that puerperal retention must arise by one of three mechanisms.

(1) Failure to initiate voiding by contracting the abdominal muscles and relaxing the pelvic floor.

(2) Paralysis of the nerves to the bladder, or central nervous inhibition, either of which results in the detrusor muscle failing to contract and to open the internal urethral meatus.

(3) Active contraction or spasm of the voluntary external urethral sphincter which, according to Roberts (1953), is normally powerful enough to resist the expulsive action of the bladder detrusor.

These various possibilities were studied by means of urethro-cystography carried out on 40 women who failed to void within 24 hours of delivery. The radiation dose to the gonads was reduced to a minimum by never allowing more than one exposure, and by making it at a time when the ovaries are still situated at a high level beside the recently delivered uterus. To ensure that these organs were kept outside the area of direct irradiation, a small X-ray cone was used and the field of investigation limited to the urethra and bladder base.

The women investigated fall into two groups:

(i) *Thirty primiparae who had been delivered vaginally.* All these had a perineal laceration or episiotomy incision sutured. All except 5 had had a forceps or assisted breech delivery.

(ii) *Ten patients who had been delivered by lower segment Caesarean section.*

Group (i). The findings were constant in all the 30 women who had been delivered vaginally. The process of voiding was initiated normally in every case; the bladder detrusor contracted, the posterior urethro-vesical angle disappeared and the upper urethra opened. Always, however, the stream of fluid was arrested at the level of the urogenital diaphragm (Fig. 14), giving rise to radiographs which are identical with those obtained when the normal woman voluntarily arrests micturition by contracting the external urethral sphincter (Fig. 13d). It is established that spasm of the levatores ani and sphincter ani muscles commonly results in spasm of the external urethral sphincter, the innervation of these groups of muscles being similar or closely connected. It would therefore seem likely that the primary cause of retention in these cases is the injured and painful perineum causing reflex contraction of the voluntary muscle around the lower urethra. This is not to deny that other factors may contribute. Thus, the woman who is in an unnatural posture and who is nervously tense may find it more difficult than another to relax the spastic external urethral sphincter. Irrespective of the causal factors concerned, however, the retention is caused by spasm of the voluntary muscle at the lower end of the urethra. The voiding processes otherwise operate normally. This is the common mechanism of urinary retention seen after childbirth.

Group (*ii*). The findings in the women who suffered urinary retention after Caesarean section were different. In all 10 cases radiographs taken during an attempt to void showed a failure to initiate the mechanism. The detrusor muscle of the bladder did not contract and the internal meatus did not open. The whole bladder and urethra remained quiescent (Fig. 15). This inertia could be a manifestation of central nervous inhibition, of failure of the trigger mechanism believed to be related to contraction of the abdominal muscles, or of a local disturbance of the autonomic nerve fibres during mobilization of the bladder at operation.

Conclusions

The observations recorded here, although primarily concerned with retention of urine as it occurs during pregnancy and the puerperium, have a wide application to obstetrics and gynaecology. They indicate that there are three possible mechanisms whereby urinary retention occurs in women.

(1) *Failure of the Bladder Detrusor Muscle to Contract and to Open the Upper Urethra*

This occurs:

(*a*) When the patient fails to contract the abdominal muscles to initiate the process of voiding. This is likely after any abdominal operation, either gynaecological or obstetrical, and is dependent on pain and fear.

(*b*) When the detrusor muscle is inhibited by emotional disturbances of various kinds. This is seen in conditions of hysteria and may sometimes be an additional factor in post-operative retention.

(*c*) When the excitatory nerves to the detrusor are paralysed by lesions of the central nervous system or by local nerve injury sustained during operations involving extensive dissection around the bladder base. The latter is illustrated by urinary retention which commonly follows Wertheim's hysterectomy.

(*d*) When the bladder muscle becomes over stretched and atonic as a result of the neglect of retention originating by any other mechanism.

(2) *Spasm of the Voluntary External Urethral Sphincter Arresting the Outflow of Urine at the Lower End of the Urethra*

This is mainly an accompaniment of spasm in the levatores ani and sphincter ani muscles and occurs:

(*a*) With perineal injuries sustained during childbirth.

(*b*) After vaginal plastic operations, especially perineorrhaphy (Fig. 16).

(3) *Mechanical Interference with the Normal Obliteration of Posterior Urethro-vesical Angle which is Essential to the Opening of the Upper Urethra*

This occurs:

(*a*) When any tumour is impacted in the pelvis. Examples include the retroverted gravid uterus, the foetal head during late labour and a fibroid or ovarian cyst in the non-pregnant woman.

(*b*) When the vagina is packed tightly for some purpose such as the arrest of haemorrhage or the maintenance in place of radium containers.

(*c*) After operations designed to buttress and support the urethra and bladder base in cases of stress incontinence (Fig. 17).

(*d*) When a urethral sling is made too tight or when urethrocystopexy (Marchetti operation) is carried out with too much enthusiasm (Fig. 18).

Summary

(1) Approximately 80 per cent of women (primigravidae and multigravidae) experience frequency of micturition at some time during pregnancy. This symptom is usually progressive and rarely shows an intermission in mid-pregnancy.

(2) The frequency of pregnancy is present by night as well as by day and is not related to the woman's posture or activity.

(3) In late pregnancy there is some evidence that the bladder is more irritable and its capacity reduced. At other times there is no change in bladder tone and tolerance; pregnancy frequency is then the result of polyuria.

(4) The polyuria of pregnancy is related to an increased intake of fluid but it is not known which is the cause and which the effect.

(5) The impacted retroverted gravid uterus causes retention because it interferes with the obliteration of the posterior urethro-vesical angle. It does not elevate the urethro-vesical junction in the pelvis nor does it elongate the urethra. Impacted pelvic tumours in the non-pregnant woman act similarly.

(6) Retention of urine which follows vaginal delivery (and plastic operations) is usually the result of spasm of the voluntary external urethral sphincter, the voiding mechanism being otherwise normal. This spasm is mainly caused by painful lesions of the perineum and peri-anal area.

(7) Retention of urine following Caesarean section (and other abdominal operations) is usually explained by a failure of the detrusor muscle of the bladder to contract. This may be because the patient does not contract her painful abdominal muscles, although central nervous inhibition and local interference to nerve supply of the bladder are other possible factors.

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ACUTE COAGULATION DISORDERS AT PARTURITION

A Scheme of Laboratory Investigation, with Illustrative Case

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THERE is now an extensive literature on the acute coagulation disorders which may complicate pregnancy and parturition. Simple diagnostic clotting tests have been proposed, but the laboratory aspects of clinical management have not been discussed in comparable detail.

These emergencies may, of course, occur where laboratory facilities are not fully available, but, given the opportunity, the clinical pathologist in consultation may be able to provide much information of value to his obstetrical colleague. It is the purpose of this paper to suggest a basic scheme of laboratory investigation to determine the nature and extent of the haemostatic defect and to follow its course. Clear indications for replacement infusion will then be available, the fate of the transfused material may be followed and the beginning of the recovery of haemostasis will be apparent.

REVIEW OF THE LITERATURE

Early Observations

In his *Experimental Inquiry into the Properties of the Blood* . . . Hewson (1771) mentions a woman whom he saw "by the courtesy of Dr. Huck and the physicians of the British Lying-In Hospital, who having bled a woman in a fever that came on soon after delivery, found that the blood did not coagulate". Hewson examined this blood, and made the profound observation that on heating it behaved like serum: that is, it did not solidify until the temperature reached 160° F. (*c.* 70° C.). He therefore concluded that it might have been "without the coagulable lymph", or what we would call fibrinogen, which is precipitated at about 130° F. (55° C.). Nevertheless, when the woman came to autopsy three days later, clot was found in the vessels, showing that the afibrinogenaemia had been transitory. DeLee (1901) and Dieckmann (1936) reported cases of abnormal bleeding at the time of delivery, both associated with *abruptio placentae*, and Dieckmann again described the deficiency of fibrinogen.

Bleeding states have since been encountered in association with abortion, concealed antepartum haemorrhage (*abruptio placentae*), amniotic fluid embolism (often associated with tumultuous labour), retained dead foetus and hydatid mole. There is often an associated shock and there may also be a degree of toxaemia. The most obvious coagulation defect is the decreased fibrinogen concentration, but associated deficiencies of other coagulation factors have also been described.

Three principal mechanisms have been thought to cause these disorders. First, a process of intravascular clotting might exhaust the maternal circulation of "consumable" coagulation factors ("defibrination syndrome");

alternatively, these and perhaps other factors might be destroyed by an activation of the fibrinolytic system; or, third, a powerful anticoagulant might be released into the mother's blood so that clotting would be prevented. In addition, it has been suggested that very rapid utilization (e.g. haemostasis at the placental site), or, in a sick woman, insufficient synthesis of clotting factors, might be responsible.

The evidence for these views on causation will be briefly considered since the picture is complicated by the varied associations of clinical states and haematological processes which have been reported, and it is important to know what abnormalities have already been encountered, and in what circumstances.

First, it may be useful to summarize the sequence of changes which occur when blood clots.

Three stages may be recognized. The first, and longest, leads to the formation of thromboplastin; among other factors, *Christmas factor*, *antihaemophilic globulin* (AHG), *platelets* and *factor V* are involved. In the second stage, thromboplastin converts *prothrombin* to thrombin; and, in the third stage, thrombin changes *fibrinogen* into fibrin. When blood is mixed with tissue juice, clotting is greatly accelerated, because in the first stage thromboplastin is formed by a different, more rapid, process. This requires *factor VII* but not AHG and platelets, although these components are often incidentally destroyed by the thrombin subsequently liberated. The two mechanisms may be said to lead to the activation of "blood thromboplastin" and "tissue thromboplastin" respectively. The italicized components are normally present in blood, which also contains an analogous series of factors which on interaction produce a powerful proteolytic enzyme called fibrinolysin. This can attack various clotting factors.

The mechanisms of bleeding will now be reviewed.

(1) *The Reduction of Clotting Factors by a Process of Intravascular Clotting*

It is supposed that coagulant material escapes from the conceptus into the maternal circulation and causes rather gradual but widespread clotting throughout the mother's blood. The fibrin is filtered off by the capillary bed (particularly in the lungs) and the red cells continue to circulate suspended in serum.

In animals, Wooldridge (1886) found that the blood became incoagulable when tissue extract was slowly infused. Gutmann (1914) and Mills (1921) published evidence that this was associated with a fall in the plasma fibrinogen concentration. Schneider and Engstrom (1954) noted an accompanying fall in prothrombin and factor V activity and in the platelet count (characterizing the conversion of blood into a suspension of red cells in serum) and at the same time noted that the arterial pressure rose in the pulmonary circulation and fell in the systemic, producing a state of shock; Brinkhous and Penick (1955) found an associated fall in the activity of the plasma antihaemophilic globulin; and Johnstone and McCallum (1956) noticed the development of a haemorrhagic tendency and demonstrated fibrin-like emboli in the lungs. In a pregnant rabbit, Schneider (1950) reproduced similar pulmonary lesions by mechanical interference with the placenta, and Anderson and Johnstone (1956) found similar changes in an iso-immunized doe which died suddenly in giving birth to a hydropic foetus. Hidalgo (1952) produced hypofibrinogenaemia in muscle-crushing experiments, and the work of Penick, Roberts, Webster and Brinkhous (1958) suggests that the infusion of tissue substance leads to the production of "blood thromboplastin" as well as of "tissue thromboplastin", thus explaining the widespread depletion of clotting factors observed.

In a pregnant woman dying soon after the development of *abruptio placentae*, Schneider (1951) described emboli of fibrin-like material blocking the pulmonary arterioles; and in a similar case with comparable emboli Johnstone and McCallum (1956) found post-mortem that the heart blood was unclotted and afibrinogenaemic. In cases of *abruptio placentae*, a fall in the platelet count was reported by Hodgkinson, Margulis and Luzadre (1954) and lowered activities of factor V by Johnson, Seegers and Braden (1952), factor VII by Masure and Schockaert (1954), and tentative evidence of antihaemophilic globulin deficiency by

Greenwalt and Triantaphyllopoulos (1954). Definite evidence for the latter was given by Sharp, Howie, Biggs and Methuen (1958).

Mills (1921) and Seegers and Schneider (1951) reported that placenta and decidua were unusually rich in clot-promoting substance. In the puerperium, Barnes (1947) had found the normal post-partum blood loss to be defibrinated and to accelerate clotting to the same extent as defibrinated venous blood; and Masure and Schockaert (1954) noted that it possessed an ability to shorten the clotting time of venous blood equivalent to that of tissue extract.

Schneider (1952) worked out the "pathway of auto-extraction" whereby material could reach the maternal circulation from the site of detachment in *abruptio placentae*; and Mayer, Dreyfus and Bugnard (1954) found confirmatory evidence in extensive fibrinous masses occluding the vessels (principally veins) of uteri obtained from fatal cases of *abruptio placentae*, associated with diffuse fibrinous occlusion of small vessels in the lungs and other organs.

The syndrome has been observed as early as the 19th week of pregnancy (Blakey, 1959); and Boyd (1958) found similar lesions in the lungs of two infants at whose births there had been evidence of abnormal maternal bleeding.

Defibrination has also been recognized as a complication of thoracic surgery, and Ingram and Mann (1959) reported a fall in the Christmas factor in such a case, among other clotting defects.

(2) *The Reduction of Clotting Factors in Association with Fibrinolysis*

It is supposed that fibrinolytic activity develops in the maternal circulation to an extent sufficient to destroy the circulating fibrinogen, as well as other clotting factors.

Willson and Munnell (1946) found evidence of moderate fibrinolysis in two cases of *abruptio placentae*. Many similar observations have since been made linking fibrinolysis with a marked reduction in plasma fibrinogen concentration in obstetric emergencies complicated by abnormal bleeding which may be severe and generalized. Besides *abruptio placentae* these conditions include retained dead foetus (Weiner, Reid, Roby and Diamond, 1950), amniotic fluid embolism (Ratnoff and Vosburgh, 1952) and criminal abortion (Soulier, Petit and Le Bolloch, 1952). In fibrinolytic states associated reductions have also been noted in the platelet count (O'Driscoll and Lavelle, 1955), prothrombin activity (Weiner, Reid and Roby, 1950), factor V (Soulier *et al.*, 1952) and indirect evidence for a reduction in AHG (Greenwalt and Triantaphyllopoulos, 1954).

Similar bleeding states associated with acute fibrinolysis are, of course, known in other fields: for instance, in pulmonary resection (Mathey *et al.*, 1950; Soulier *et al.*, 1952) and in surgery of the pancreas (Ratnoff, 1952) and of the prostate (Rollason and Shillitoe, 1954). The disease may rarely occur spontaneously (Firkin, Reed and Blackburn, 1957). Fibrinolysis was extensively studied and reviewed by Macfarlane and Biggs (1948) and its clinical associations have been reviewed by Frick (1956), Kellock and Gallagher (1958) and Cooper (1959).

Fibrinolysin artificially prepared from blood has *in vitro* the properties of a proteolytic enzyme, destroying fibrin and fibrinogen (Kaplan *et al.*, 1942; Tagnon, Davidson and Taylor, 1942), prothrombin (Seegers and Loomis, 1946) and factor V (Alagille and Soulier, 1956). When infused, it leads to a fall in fibrinogen concentration and in the activities of factors V and VII, and to a reduced activity of the plasma in the thromboplastin generation test (Coon and Duff, 1958). There is evidence that the endometrium may develop a powerful fibrinolysin (Smith, 1947) and that the normal post-partum blood loss possesses this property (Barnes, 1947). Activators of the fibrinolytic system of the circulating blood have been reported from macerated tissue (Lewis and Ferguson, 1952), and in amniotic fluid (Albrechtsen and Trolle, 1955). It thus seems likely that the fibrinolytic system might be activated by the escape of material from the conceptus into the maternal circulation, on the lines proposed in the previous section.

(3) *Incoagulability Following the Release of an Anticoagulant*

It is recognized that bleeding disorders may arise in association with pregnancy owing to the development of anticoagulants which show some

of the characteristics of auto-antibodies (Biggs and Macfarlane, 1957, pp. 302–312). Such conditions are of rather gradual onset and indeed may only appear some weeks or months after delivery.

In addition, acute haemorrhagic states may arise at the time of delivery, in association with an anticoagulant having the properties of heparin. Willson (1922) drew attention to the similarity between the generalized bleeding state which might accompany obstetric accidental haemorrhage and the effect of the venom of certain snakes: he thought that in the obstetric condition an "inhibition of coagulation" might be present; and Thompson (1948) suggested that heparin might be released in toxaemia of pregnancy associated with a bleeding tendency. Laboratory evidence of heparinaemia has been obtained in cases of septic abortion (Conley, Ratnoff and Hartmann, 1951), amniotic fluid embolism (Ratnoff and Vosburgh, 1952), *abruptio placentae* (Masure and Schockaert, 1954) and manual removal of the placenta (Jürgens and Stein, 1954) associated with abnormal bleeding.

Experimentally, in dogs, Ratnoff and Conley (1951) found evidence of the release of a heparin-like substance following intravenous injection of tissue extract, and Schneider (1953, 1955) found that the "shock" produced by infusion of meconium was accompanied by a powerful release of heparin.

(4) *Excessively Rapid Utilization of Clotting Factors*

FitzGerald and Jackson (1956) estimated the fibrin content of the clot evacuated from the uterus at the time of delivery of the placenta in a case of accidental haemorrhage, and obtained the astonishing figure of 63 grams. Even if this were a considerable over-estimate, owing to the unavoidable inclusion of much other protein (Morrison, 1947) it must have represented no mean drain on both the circulating fibrinogen and the capacity of the body to regenerate it, and also on the other clotting factors consumed in the coagulation process.

Further references will be found in the reviews of Schneider (1954, 1955, 1956), Jackson, Hartmann and Busby (1955), Larkin and Philipp (1956) and Tuller (1957).

Summary

In pregnancy and childbirth, an acute bleeding state may arise from various different causes, but the nature of the haemostatic defect cannot be predicted from the clinical picture. The laboratory investigation of a case must therefore allow for the various possibilities which have so far been observed.

Proposed Laboratory Procedures

The literature reviewed above suggests that a generalized bleeding state may arise through the liberation of a heparin-like anticoagulant, the activation of the fibrinolytic system or by "defibrination". In these three conditions, the pathological process goes forward in the circulating blood, and so may readily be investigated in blood samples from a peripheral vein; the proposed tests are therefore planned on this basis. It is clearly less easy to draw conclusions from peripheral blood in bleeding states arising solely from excessive utilization or defective synthesis of clotting factors, except in so far as the resulting deficiencies may be detected—information which will be given by the tests irrespective of the cause.

Principle

If a heparin-like substance is present, this may alter the conclusions to be drawn from clotting tests. The first step is, therefore, to measure the thrombin clotting time, adapted as a test for heparin activity. If this test is positive, it is then modified to provide an approximate assay of the circulating anticoagulant, as a guide to the dose of protamine* required to neutralize the heparin, following which the tests would be repeated. If the test for heparin is negative, or when it has been neutralized, the plasma is tested for fibrinolytic activity, and also for evidence of the consumption of coagulation factors, viz., lowered or unclottable plasma

* Protamine may shortly be superseded by a new anti-heparin agent—"Polybrene" (Preston and Parker, 1953; Preston, Hohf and Trippel, 1956).

fibrinogen, prolonged prothrombin time and diminished ability to generate thromboplastin. If fibrinogen or other replacement infusions are given, appropriate tests may be repeated to judge their efficacy and the need for further doses.

It is assumed that the tendency to bleed is of acute onset: if there is reason to suspect the pre-existence of a bleeding disease, the investigation should follow the appropriate lines (Biggs and Macfarlane, 1957, pp. 379–385).

Reagents

The following may be required:

(1) Trisodium citrate 3·8 per cent; calcium chloride M/40; tissue extract (e.g., brain), as for routine prothrombin times (Biggs and Macfarlane, 1957, pp. 386, 394).

(2) Platelet substitute and buffer for the thromboplastin generation screening test (Hicks and Pitney, 1957).

The brain extract recommended by Hicks and Pitney may be replaced by a commercial soy-bean phospholipid "Inosithin" (Associated Concentrates Inc., 57-01, 32nd Avenue, Woodside, N.Y.), in a 20 mg. per cent suspension. A 1 g. per cent suspension keeps for weeks or months at −20° C., from which the 1:50 working suspension can be prepared. This should be maintained in ice during tests and renewed after about 4 hours.

Since veronal has been found to interfere with the generation of blood thromboplastin (Biggs, Eveling and Richards, 1955), Gomori's "*tris*" buffer, amino*tris*(hydroxymethyl)methane (Gomori, 1946) pH 7·4, M/20, which does not inhibit enzymes and which is rather less expensive than glyoxaline (imidazole), may be used.

(3) Fibrinogen and thrombin solutions—fibrinogen may be prepared from normal plasma by salt-precipitation (Biggs and Macfarlane, 1957, p. 389) and thrombin is available commercially. Fibrinogen: a stock solution, 1 g. per cent, containing 25 per cent Owren's buffer (Owren, 1949; *vide* Hicks and Pitney, 1957, *supra*) has been found to keep indefinitely at −20° C.; two working solutions, 200 mg. per cent are made in "*tris*" buffer, with and without 10 per cent of normal plasma. Thrombin: a stock solution 50 u./ml., in "*tris*" buffer, is stable at −20° C.; for the working solution, this should be diluted until 0·2 ml. clots 0·1 ml. of normal citrated plasma in about 15 seconds: the diluent is a mixture of equal volumes of "*tris*" buffer and M/40 calcium chloride solution. This solution is calcified because in certain tests the fibrinogen solution receives an addition of normal plasma, since the reaction between thrombin and fibrinogen is affected by the presence of both calcium ion (Robbins, 1944) and plasma protein (Shinowara, 1949), the latter being especially important in the heparin tests. These working solutions may also be stored frozen for short periods. They should be checked against each other and replaced when the clotting time begins to lengthen.

(4) Heparin solutions: dilutions may be made up *passim* from an ampoule of Injection of Heparin, B.P.: great accuracy is not required. Toluidine blue: working solution 50 mg. per cent.

Blood Samples

The suggested tests are all performed on citrated plasma. Mix 13·5 ml. blood with 1·5 ml. 3·8 per cent trisodium citrate solution; samples for the haematocrit of the citrated blood (for fibrinogen estimation) and for the platelet count (if not made directly from the patient) are withdrawn, and the remainder is centrifuged sufficiently to remove the great majority of the platelets, to yield citrated plasma.

In addition, normal citrated plasma is required for control tests, and for the second stage of the thromboplastin generation screening test.

Order of Testing

Test 1. Thrombin clotting time (for free heparin). To 0·1 ml. plasma add 0·2 ml. thrombin solution, and record the clotting time. If the patient's clotting time does not exceed the control time by more than one-fifth as much again, there is unlikely to be a significant quantity of a heparin-like anticoagulant present. If in doubt, repeat with the thrombin solution further diluted so as to double the control clotting time. In the presence of heparin, the

patient's clotting time would be proportionately longer in relation to the control.

If this test is normal, proceed to Test 6.

If the patient's clotting time is prolonged or if the patient's clot appears thin or small, proceed to Test 2.

Test 2. Thrombin clotting time with added fibrinogen. To 0·1 ml. plasma add 0·1 ml. fibrinogen solution without added plasma and then proceed as for Test 1, taking new control readings with fibrinogen added to the normal plasma also.

If the patient's clotting time is now normal, the prolongation in Test 1 may be ascribed to fibrinogen deficiency: proceed to Test 6. If the patient's clotting time is still prolonged, proceed to Tests 3, 4 and 5.

Test 3. Thrombin clotting time with mixture of patient's and control plasma (general test for anticoagulant in patient's plasma). Repeat Test 2 with 0·1 ml. of a 50:50 mixture of patient's and control plasma. If the clotting time is lengthened (over control plasma alone), to an amount commensurate with the abnormality found in the patient's plasma in Test 2, this confirms the presence of an anticoagulant.

Test 4. Thrombin clotting time with toluidine blue: confirmatory for heparin. (*i*) To 0·1 ml. plasma add 0·1 ml. toluidine blue solution, and proceed again as for Test 1. (*ii*) If patient's clotting time is not appreciably less prolonged by (*i*), combine Tests 2 and 3, i.e., add both fibrinogen and toluidine blue to both plasmas. If by either procedure the patient's clotting time is brought nearer to the corresponding control clotting time, this confirms the presence of a heparin-like anticoagulant. Note that the addition of toluidine blue may prolong the control clotting time. This does not matter. The neutralization of heparin is shown by reducing the difference between the patient's and the corresponding control clotting times.

Test 5. Approximate assay of circulating heparin-like anticoagulants. Principle: The prolongation of the thrombin clotting time by (dilutions of) the patient's plasma is compared with that produced by a known dilution of heparin. Method: using the technique of Test 2, find that dilution of patient's plasma (say 1 in x) in "*tris*" buffer which approximately doubles the thrombin clotting time when 0·1 ml. is added to 0·1 ml. of the fibrinogen solution containing 10 per cent normal plasma; then find that concentration of the known heparin solution (say 1 in y) which gives a similar prolongation; a greater increment in clotting time may blur the end-point. It may then be concluded that 1 in x plasma contains about the same concentration of heparin-like activity as 1 in y heparin solution. If the potency of the starting solution of heparin is h u./ml., the inhibitory activity of the patient's plasma will be equivalent to hx/y u./ml. of heparin. The total circulating anticoagulant is calculated as mg. of heparin.

Method: (*i*) Assess the patient's blood volume as 10 per cent of pregnant body weight, an estimate accurate enough for this purpose, although the true value is probably nearer 9 per cent (Dieckmann, 1941). (*ii*) Assume plasma volume is half the blood volume. (*iii*) The circulating anticoagulant is then roughly equivalent to plasma volume (in ml.) $\times$ $hx/100\,y$ mg. (since the potency of heparin is of the order of 100 u./mg.). The patient may then be given the same weight of protamine sulphate intravenously. Example: known heparin solution, injection of heparin, B.P., 5,000 (h) u./ml.; equivalent prolongations of clotting time produced by plasma 1/50 (1 in x) and heparin 1/20,000 (1 in y); patient's weight 55 kg. (whence plasma volume 2,750 ml.)

$$\frac{\text{plasma vol.} \times hx}{100\,y} = \frac{2{,}750 \times 5{,}000 \times 50}{100 \times 20{,}000} = 344 \text{ mg.}$$

total circulating heparin. Dose of protamine sulphate therefore 344 mg. or 34 ml. of a 1 per cent solution.

Tests 2–5 may be repeated as necessary until the heparin-like activity has been neutralized. (Clearly the calculation takes no account of extra-circulatory heparin.) Then proceed to Test 6.

Test 6. Fibrinogen determination and conventional fibrinolysis test. Set up, each in duplicate, from both patient and control, mixtures of equal volumes (say 3·0 ml.) of plasma and calcium chloride solution, and incubate at 37° C. After about 10 minutes harvest the fibrin from one tube from each plasma by winding the clots on to wooden

swab-sticks, and stand the sticks in other tubes containing distilled water for another five minutes. Then re-examine the tubes from which the fibrin has been taken, and harvest any further clot: repeat until no more clot forms (in fact, clotting is usually complete at the first harvesting). Leave the other pair of tubes to incubate: examine periodically for evidence of dissolution of the clots. If lysis is not visible after a number of hours (e.g., 12 or 24 hours) harvest the fibrin for determination as before. Compare the proportionate losses of fibrin from patient and control samples over the period of incubation.

If no clot forms in the patient's plasma on recalcification, the test may be repeated, adding to each of the four tubes a volume of the fibrinogen solution without added plasma. The results will allow an assessment of fibrinolytic activity; and if clotting now occurs normally in the patient's tubes, the afibrinogenaemia of the patient's plasma is confirmed.

Note that normal plasma may lose up to *c.* 30 per cent of fibrin on incubation for 24 hours (Adelson and Roeder, 1958).

Determination: Peel the clots off the sticks, press out the water between filter-papers and dehydrate in about 5 ml. of acetone for ten minutes. Transfer each clot to the palm of the hand and vaporize the residual acetone by gentle blowing. Weigh the clots to $\pm 0{\cdot}2$ mg. The calculation is as follows:

$0{\cdot}1 \times$ clot weight (mg.)/plasma volume used (ml.)=fibrinogen concentration (g./100 ml. plasma).

This will give an approximate result which may be refined by applying two corrections: (*i*) Correction for retained water: decrease the clot weight by subtracting 15 per cent of the observed weight, and, in addition, a further $\frac{1}{2}$ per cent for each mg. (e.g., for a clot of 30 mg. subtract in all 30 per cent or 9·0 mg.). (*ii*) Correction for the dilution of the plasma with citrate: increase the clot weight by multiplying by the improper fraction (plasma volume per cent)/(plasma volume per cent−10 per cent). These values are obtained from the haematocrit of the citrated blood.

Example: 3·0 ml. citrated plasma in each tube. Ex acetone clot weights before incubation: control 10·4 mg., patient 4·0 mg.; after incubation for 15 hours, control 9·8 mg., patient 2·2 mg. Haematocrits of citrated blood: control 43 per cent, patient 38 per cent. Calculations:

(*i*) Patient's fibrinogen concentration. Uncorrected, $0{\cdot}1 \times 4{\cdot}0/3{\cdot}0 = 0{\cdot}133$, say 0·13 g. per cent to 2 significant figures. Corrections: for retained water, $\frac{1}{2}$ per cent $\times 4 = 2$ per cent, 15 per cent + 2 per cent = 17 per cent, 17 per cent of 4·0 mg. is approximately 0·7 mg., corrected clot weight therefore 4·0 − 0·7 = 3·3 mg.; from haematocrit, 100 − 38 = 62 per cent; proportion of citrate solution in citrated blood = 10 per cent; therefore multiply by 62/(62 − 10). Corrected value therefore $0{\cdot}1 \times 3{\cdot}3/3{\cdot}0 \times 62/52 = 0{\cdot}131$ g. per cent. In this case the two corrections have nearly cancelled each other, which will tend to happen with the lower fibrinogen concentrations (giving small clots which are reasonably dry after only 10 minutes in acetone). In severe reductions in fibrinogen concentration the corrections are therefore less important, so that for diagnostic purposes the corrections are usually unnecessary, but may be applied after giving fibrinogen, to test the observed level against expectation.

(*ii*) Fibrinolysis test. Clot weights corrected for retained water:—control: before incubation, 8·3 mg., after incubation, 7·9 mg., loss 0·4 mg. or approximately 5 per cent; patient: before incubation, 3·3 mg., after incubation, 1·8 mg.; loss 1·5 mg. or approximately 45 per cent.

It will be apparent that the arithmetic is largely proportional and may readily be computed by slide rule.

As soon as the four tubes have been put to incubate, proceed to Test 7.

Test 7. Prothrombin time (principally for factor V). Compare the patient's with the control plasma in the usual manner. If Tests 2 and 6 suggested a reduction in fibrinogen concencentration, add the fibrinogen solution without added plasma to both samples as in Test 2. Use 0·1 ml. volumes. Harvest the clots from the first pairs of tubes in Test 6, and then proceed to Test 8.

Test 8. Thromboplastin generation screening test (principally for antihaemophilic globulin: after Hicks and Pitney, 1957). Dilute 0·1 ml. volumes of patient's and control plasmas to

1/10 with "*tris*" buffer. For the test, mix 0·3 ml. dilute plasma, 0·3 ml. inosithin suspension and 0·3 ml. calcium chloride solution. Sample this reaction mixture at 2, 3, 4, 5, 6 and 7 minutes by adding 0·1 ml. to 0·1 ml. control plasma (which serves as an "external indicator" of thromboplastin activity) with 0·1 ml. calcium chloride solution and note the clotting time. The control reaction should give indicator clotting times of about 10 seconds (or less) towards the end of the series. A deficiency of AHG and (to a lesser extent of factor V; Hörder and Sokal, 1955; Hicks and Pitney, 1957) is shown if the indicator clotting times from the patient's reaction do not shorten so much as those from the control reaction.

Any citrated plasma remaining may be returned to the refrigerator and examined from time to time. If fibrin gradually forms, this suggests that the blood contained traces of thrombin or a proteolytic enzyme with similar properties which might be fibrinolytic (Tagnon *et al.*, 1942) at the time of citration. This procedure is analogous to the "test for the beginning of thrombin generation" which was used by Forwell and Ingram (1957).

Alternative test for fibrinolysin. If, on incubation of citrated plasma (with added fibrinogen if necessary), serial thrombin clotting times (Test 1) show a considerable and progressive lengthening during an hour or so in the patient's plasma only, this is presumptive evidence of active destruction of fibrinogen (Wilhelm, Miles and Mackay, 1955). This test may be more convenient since it is easier to fit in with other work, and we have found it useful.

Discussion of the Tests

These tests are arranged so that the possibility of heparinaemia is considered first, since heparin would affect subsequent tests. If the thrombin test (Tests 1 and 2, which take only a few minutes) is normal, or becomes normal on the addition of fibrinogen, there are then, besides the platelet count, three simple stages: the estimation of fibrinogen and the fibrinolysis test, the prothrombin time (to which fibrinogen may be added) and the thromboplastin generation screening test. The fibrinogen estimation involves two waiting periods of ten minutes, during which the prothrombin times may be done and the platelet count (which by then will have settled) may be enumerated.

Provided that reagents can be maintained at −20° C. as suggested, and are therefore always ready for use, all these tests can be performed by one person in less than one hour from receiving the blood samples, and the need for concentrated fibrinogen will be apparent in about half that time.

The clotting time of whole blood is not included among the tests proposed because this may be nearly normal in the face of a considerable haemostatic failure, even in obstetrical cases (Sharp *et al.*, 1958). This is not to belittle the importance of noticing defective clotting in routine blood samples, for cases will sometimes present in this way (Bourne and Riedel, 1958).

Tests 1–5. There are two characteristic features of the effect of heparin upon the rate of the reaction between thrombin and fibrinogen.

If the fibrinogen concentration is constant, and the concentration of thrombin and heparin are varied, a series of curves relating clotting time to thrombin concentration may be plotted for various heparin concentrations. This family of curves is not parallel, but spreads fanwise from the effective origin. Good examples are given by Wenckert and Nilsson (1955). Thus, if two plasmas (one of which contains heparin) are tested with two or more dilutions of thrombin, the lower the thrombin concentration the greater will be the relative difference between the clotting times of the two plasmas. This distinguishes the effect of heparin from that due to an abnormality of fibrinogen, as in Ingram's (1955) second case. The heparin effect is well seen in the obstetric cases investigated by Ratnoff and Vosburgh (1952) and Jürgens and Stein (1954).

It is also characteristic that this effect may be reversed by toluidine blue or protamine. Examples are given by Quick and Hussey (1957) in a case of severe post-partum bleeding, and in other contexts by Allen and Jacobson (1947), Speer, Hill, Maloney and Roberts (1955), Nussey and Dawson (1957), and Cetingil, Ulutin and Karaca (1959). These reports illustrate the investigation and treatment of bleeding conditions associated with heparin-

aemia. To neutralize heparin *in vivo* it is necessary to know approximately how much is circulating so as to calculate the dose of protamine sulphate, which itself acts as an anticoagulant in excess.

Sharp *et al.* (1958) described three obstetrical cases with acute coagulation disorders, in which the thrombin clotting time was grossly prolonged although the fibrinogen concentration was not greatly reduced at the material time and the test for an anticoagulant was negative. The significance of their findings is not entirely clear, but their observations are reminiscent of Kowalski's experiments on "antithrombin VI", an inhibitor of the thrombin-fibrinogen reaction, believed to be derived from fibrinogenolysis. The Polish work is summarized in English by Kowalski, Kopeć and Niewiarowski (1959) and Niewiarowski, Kowalski and Stachurska (1959).

Error of the method. Expressed as the coefficient of variation, the experimental error of the thrombin clotting time test has been assessed at about 5 per cent (Ingram and Armitage, 1952) but is likely to rise in the presence of heparin.

Test 6. (i) *Fibrinogen determination.* The classical gravimetric determination of clot (Scudamore, 1824) is proposed for the following reasons:

(*a*) It is thought better to estimate clottable material than a salt precipitate, since we have found that plasma defibrinated by thrombin to the point where no further clot forms will still give a precipitate at one-third saturation with ammonium sulphate; (*b*) in mixtures of whole and defibrinated plasma, clot weight has been found more reliable than salted-out turbidity at low fibrinogen concentrations (which may be important in following the progress of a case) contrary to the good reports of turbidity measurements by Parfentjef, Johnson and Cliffton (1953) and Coles and Roman (1957); and (*c*) a weighing can be performed by persons without chemical training; and after ordinary laboratory hours it may be simpler to arrange access to a balance (harvesting larger volumes of plasma if the available balance is of less sensitivity than suggested above) than to a micro-Kjeldahl apparatus or a photometer.

Errors of the method. Various sources of small errors have been pointed out elsewhere (Ingram, 1952), but are here ignored. The correction suggested for retained water in the rapid method was obtained from the observed loss of weight when clots, prepared as described above, were heated in air for three hours at 98° C. Thirty-one clots were tested, the initial weights ranging from 0·6–46·0 mg.; the relation between per cent loss in weight and weight ex acetone was found to be (with 95 per cent confidence limits) per cent loss=0·608 (0·318–0·898)×weight ex acetone+14·1 (8·2–20·0), with a correlation coefficient of 0·623. The correction for dilution by citrate may be important in serial samples if the patient is transfused between observations, thus altering the haematocrit.

(ii) *Fibrinolysis tests.* The time for which the clotted tubes must be observed depends on the activity of the lysin: the more powerful the lysin, the more rapidly will its effect become apparent; rapid methods for detecting weak lysins are not available. For clinical diagnosis in acute states it is likely that only the more powerful lysins are of importance (Mathey *et al.*, 1950) so that a very simple test seems sufficient: if in the conventional test the clot shows no visible change after a few hours, fibrinolysis is unlikely to be the major factor. A method using spontaneous coagulation is preferred to a technique in which the clot is formed by adding thrombin, since this is more likely to lead to lysis in normal persons (Fearnley and Ferguson, 1958).

The alternative fibrinolysis test may be more convenient to fit in with other work, but the normal range is not known; a marked effect is almost certainly abnormal.

A more detailed investigation of the fibrinolytic system may be approached in various ways. Fairly simple tests are described by Mathey *et al.* (1950) and Favre-Gilly (1952), and more detailed studies are given by Soulier *et al.* (1952), Lewis and Ferguson (1952), Albrechtsen, Storm and Trolle (1955), Phillips, Montgomery and Taylor (1957), Von Kaulla and Schultz (1958) and Heuson, Peers and Tagnon (1958). In this connexion, the diagnostic value of diminished factor V activity, which is ordinarily within the normal range at the end of pregnancy (Kennan and Bell, 1957) has been stressed by

TABLE I

Mean Values from 13 Normal Pregnancies

Observation	Mean	S.D.	Range
Age (years)	28·8	6·8	19 to 42
Days before expected date of delivery	11·4	12·2	43 to −6*
Platelet count/mm.³ blood ($\times 10^5$)	2·42	0·54	1·9 to 3·4
Prothrombin time (ratio: patient's time/control time) ..	0·918	0·062	0·79 to 0·98
Fibrinogen concentration (g./100 ml. plasma)	0·512	0·129	0·38 to 0·78

* Three pregnancies in the series were continuing beyond the expected date of delivery.

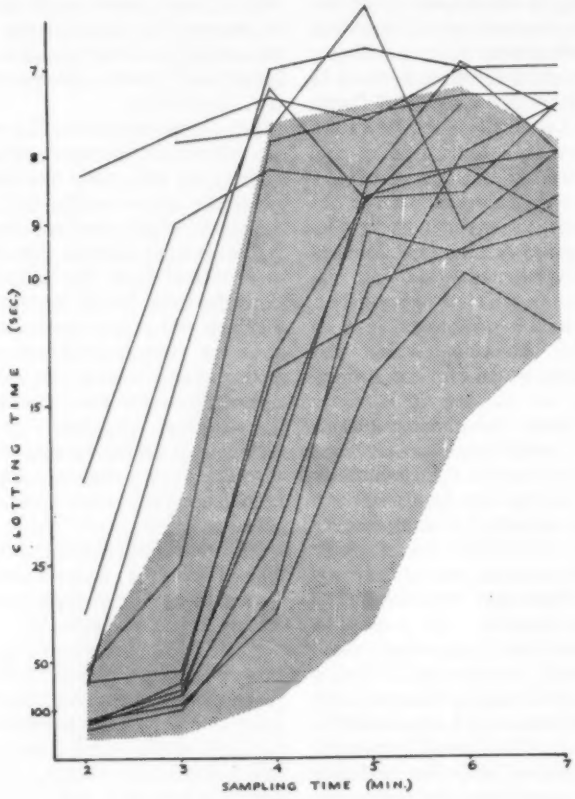

FIG. 1

Thromboplastin generation screening tests in normal pregnancy. Data from the women contributing to Table I. The limits observed in tests on eleven non-pregnant normal subjects are enclosed in the stippled area. The data were obtained on different days, with various batches of inosithin. Compare the scatter of Figure 2. Technique as described under "Test 8".

Soulier's group (Soulier, Petit and Le Bolloch, 1952; Soulier, Alagille and Larrieu, 1956).

Normal Ranges in Late Pregnancy

Normal ranges for various clotting tests made towards the end of pregnancy and in labour are given by Margulis *et al.* (1954), Ratnoff *et al.* (1954) and Kennan and Bell (1957). Our own data from 13 normal pregnancies are given in Table I and Figure 1. The platelet count is usually normal (i.e., corresponds to the non-pregnant state) in the third trimester. The thrombin-fibrinogen reaction is said also to be normal (Ratnoff, Pritchard and Colopy, 1955). The fibrinogen concentration has usually been found somewhat raised. There is very little fibrinolytic activity, even during delivery (Willson and Munnell, 1946; Smith, 1947; Margulis, Luzadre and Hodgkinson, 1954; Ratnoff, Colopy and Pritchard, 1954); indeed, Biezenski and Moore (1958) found that activity diminished steadily as pregnancy advanced. The prothrombin time has long been known to shorten (Thordarson, 1940), due to an increase in the activity of factor VII (Loeliger and Koller, 1952; de Nicola, 1952). The error of the prothrombin time is probably generally familiar; statistical assessments have been made (Armitage and Ingram, 1958).

Figure 1 suggests that the generation of thromboplastin is on the average more vigorous than normal. Hence, relatively small deficiencies in the prothrombin time and thromboplastin generation tests should be carefully examined, although it is difficult to interpret the significance of small deviations when more than one clotting factor may be involved.

As a rough guide for the thromboplastin generation test, Figure 2 shows the curves obtained from a series of non-pregnant normal plasmas diluted to one-third in haemophilic plasma. Since 30 per cent AHG seems to be about the minimum haemostatic concentration for operative intervention (Macfarlane *et al.*, 1957), it would seem reasonable to act on the assumption that the integrity of haemostasis is endangered by any combination of clotting defects producing a greater reduction in thromboplastin generation than corresponds to a one-third-normal concentration of AHG. (Note in Figure 2 that the most obvious difference between the 100 per cent and 33 per cent curves is in the delay in thromboplastin generation which the latter family show.)

Case Report

Mrs. T.H., a primigravida, aged 27 years, in the 34th week of pregnancy, was admitted at night as an emergency with the diagnosis of concealed accidental haemorrhage.

Her previous health had been good and she had been examined routinely in the antenatal clinic until 14 days before admission, when no evidence of toxaemia had been found. On admission at 9.00 p.m. on the 2nd October she complained of constant lower abdominal pain for the past 8 hours. No foetal movements had been felt since the onset of the pain, and there had been no loss of blood from the vagina.

On examination, she was in good condition though in considerable pain. The blood pressure was 120/80 mm. Hg, and the pulse rate was 96 per minute and regular. The uterus corresponded in size to a 30-week pregnancy, was hard and tender, and the foetal heart could not be heard. A specimen of urine contained no albumin. At 11.30 p.m. vaginal bleeding was first noticed. An acute coagulation disorder was suspected when blood drawn for cross-matching was found not to clot. A series of blood samples, obtained over the subsequent 24 hours, is reported in detail, with the treatment given.

First Blood Sample: 11.45 p.m.

Haemoglobin 65 per cent (Haldane).

Test 1. Thrombin clotting time. Control plasma: 12·2, 11·1 seconds; patient's plasma: 60, 58 seconds.

Test 2. Thrombin clotting time with added fibrinogen. Control plasma: 11·8, 11·0 seconds; patient's plasma: 13·0, 12·2 seconds. This was considered normal: heparinaemia was therefore excluded.

Test 6. Fibrinogen determination. 4·0 ml. plasma yielded 1·1 mg. clot; allowing 15 per cent for water, this reduced to 0·9 mg. The haematocrit had unfortunately not been determined, but was estimated from the haemoglobin as 30 per cent; this gives a fibrinogen concentration of about 0·025 g. per cent.

The fibrinolysis test was not set up on this patient.

Test 7. Prothrombin time. With added fibrinogen, control plasma: 24, 24 seconds; patient's plasma: 22, 22 seconds; normal.

The platelet count was 102,000/mm.^{3}.

Conclusion. On these results it seemed important to administer both blood and fibrinogen. Transfusion of stored blood was commenced at 11.30 p.m.; in all, 3 pints were given up to the time of delivery. The patient's weight was given as 55 kg. and her plasma volume therefore estimated roughly as 2·8 litres, which, at *c.* 0·3 g. per cent, would contain some 8 g. fibrinogen. To replace the deficit, at 12.15 a.m. on 3rd October, an infusion of 8·4 g. of fibrinogen was set up.

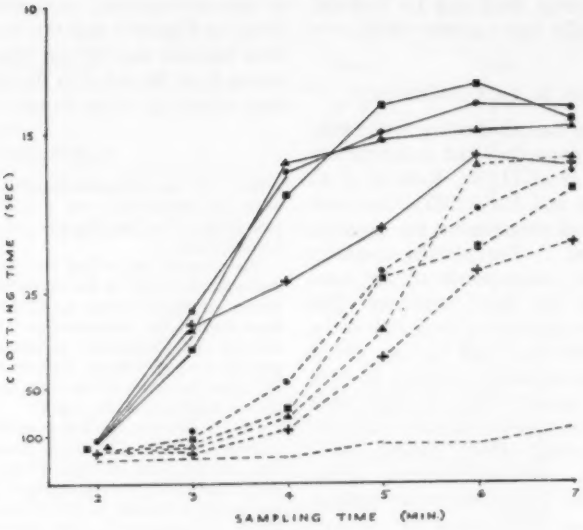

FIG. 2

Thromboplastin generation screening tests with antihaemophilic globulin reduced to one-third normal.

●–,+–,■–,▲–, Tests on 4 normal subjects.

●– –,–+–,■– –,▲– –, Tests with plasmas from the same 4 subjects, each diluted to one-third in haemophilic plasma.

– – – – – – – – – – –, Haemophilic plasma alone

Note that the plasma mixtures show a greater delay than the normal plasma before the onset of rapid generation of thromboplastin, although the two groups overlap in the final level of activity generated.

The rather long clotting times shown by these normal curves as compared with some in Figure 1 are a reflection of the lower activity of the inosithin with which the present data were obtained: these tests were, however, all made on the same day and thus show considerably less scatter than Figure 1. Technique as described under "Test 8".

Second Blood Sample: 1.15 a.m., 3rd October

Test 1. Thrombin clotting time. Control plasma: 11·9, 11·1 seconds; patient's plasma: 10·5, 10·5 seconds; normal.

Test 6. Fibrinogen determination. 4·0 ml. plasma yielded 11·2 mg. clot; allowing 20 per cent for water, this reduced to 9·0 mg. The haematocrit of the citrated blood was 21 per cent; this gives a fibrinogen concentration of 0·26 g. per cent, or about 85 per cent of expectation.

Test 7. Prothrombin time. Control plasma: 20, 20·5 seconds; patient's plasma: 19·7, 19·8 seconds; normal.

Test 8. Thromboplastin generation screening test. Shortest indicator clotting times: with control plasma in the reaction mixture: 9·5 seconds; with patient's plasma in the reaction mixture: 18·5 seconds (both at the 7-minute sampling), with about 3 minutes delay over the control time, in the rising limbs of the curves. This is clearly abnormal.

Conclusion. It was clear that fibrinogen had been satisfactorily replaced; but that there was strong presumptive evidence of AHG deficiency. Since concentrated AHG was not available, 350 ml. of fresh-frozen plasma which happened to be available were adminis-

tered. It was not at first appreciated that this had been kept at −20° C. for 9½ months, and would therefore be unlikely to have maintained its original anti-haemophilic activity.

At 3.50 a.m. further vaginal bleeding occurred.

Third Blood Sample: 11.00 a.m., 3rd October

The fibrinogen concentration had fallen to 0·14 g. per cent and the platelet count to 48,000/mm.³. In the thromboplastin generation screening test the control plasma yielded a shortest indicator time of 9·6 seconds at the 6-minute sample, whereas the patient's plasma gave 15 seconds at 8 minutes, and the patient's curve again showed three minutes delay in rising. On standing, the citrated plasma threw down a wisp of clot (there had been no difficulty at venepuncture). It was concluded that the coagulation process was continuing *in vivo*.

At 2.00 p.m. a further 4·0 g. fibrinogen were administered.

Fourth Blood Sample: 3.15 p.m., 3rd October

The haematocrit (Wintrobe) was 20 per cent; the haemoglobin (Haldane) was 42 per cent; the plasma fibrinogen concentration was 0·21 g. per cent, some 78 per cent of expectation; the shortest indicator clotting times in the thromboplastin generation screening test were 10·0 seconds for control plasma and 18·2 seconds for patient's plasma with two minutes delay. Again, clot formed in the citrated plasma after 3 hours in the refrigerator. Both the below-expectation fibrinogen concentration and the thromboplastin generation screening test suggested that the clotting process was still active: the slow clotting of citrated plasma similarly suggested that the blood still contained free thrombin.

Up to now the patient's general condition had remained satisfactory. Her blood pressure fluctuated in the region of 130/90, whilst the pulse, apart from a transitory rise to 130, continued to be steady at 100. She passed 10 ounces of urine containing a trace of albumin, but no red cells or casts, and she continued to lose a little blood *per vaginam*; the total external loss of blood since admission was estimated as approximately 40 ounces.

At 6.00 p.m., 2 pints of fresh blood taken into sequestrine (ethylene diamine tetra acetate disodium) were given in an attempt to correct the thrombocytopenia and replace blood lost. Sequestrine has been found to destroy the anti-haemophilic activity of fresh plasma, so this infusion would not have supplied AHG, but contributed some 1·5 g. fibrinogen.

At 7.00 p.m. the membranes were artificially ruptured.

Fifth Blood Sample: 8.30 p.m., 3rd October

The haematocrit (Wintrobe) had risen to 28 per cent and the fibrinogen had risen to 0·36 g. per cent, some 125 per cent of expectation; but the platelet count had fallen to 35,000/mm.³ and the thromboplastin generation screening test was still abnormal. Fibrin had deposited in the citrated plasma within 3½ hours at 4° C.

When these results were obtained, the clinical pathologist met the obstetrician in consultation, and suggested that Caesarean section would be dangerous in face of the thrombocytopenia and diminished AHG activity, but that the finding of a fibrinogen concentration higher than had been expected suggested that *in vivo* coagulation was beginning to abate; and that therefore spontaneous delivery should be awaited. This advice was accepted, despite the clinical impression that abdominal evacuation of the uterus was now the lesser risk.

Part of a further pint of fresh blood taken into acid-citrate-dextrose was then given.

Sixth Blood Sample: 12.05 a.m., 4th October

The haematocrit (Wintrobe) had risen to 31 per cent, and the fibrinogen concentration was maintained at 0·36 per cent; the thromboplastin generation screening test showed shortest indicator clotting times of 12·7 seconds and 15·2 seconds for control and patient's plasma respectively, with no delay in the latter. Nevertheless, the platelet count was still only 35,000/mm.³, and the blood urea had risen to 73 mg. per cent.

These findings were held to confirm the opinion expressed at 8.30 p.m., the improvement in thromboplastin generation being thought particularly reassuring.

At 1.50 a.m. the patient delivered herself spontaneously of a stillborn male infant, weighing 4 pounds 3 ounces, accompanied by a 12-ounce blood clot. At 2.35 a.m. the placenta was spontaneously delivered with minimal blood loss. Haemoglobin immediately following delivery was 70 per cent.

Apart from a mild urinary infection and thrombosis of the left saphenous vein, the puerperium was normal.

The Return of the Platelet Count to Normal Levels

Subsequent platelet counts were as follows: 4th October: 11.00 a.m., 54,000/mm.³; 5.30 p.m., 48,000/mm.³: 5th October: 11.30 a.m., 109,000/mm.³; 7th October: [illegible],000/mm.³; 9th October: 225,000/mm.³. This delayed return has been noted before (Jackson *et al.*, 1955).

Discussion of the Case

This case was of interest to us because the bleeding tendency was diagnosed and managed entirely on laboratory evidence. We feel it is also of more general interest as an illustration of the part which may be played by the pathologist in clinical strategy.

For this sort of co-operation, it is clearly necessary for a pathologist to be available at night; this is also apparent from the work of Sharp *et al.* (1958). The tests must be planned so that they can be carried out single-handed, and arrangements should be made for continuity over a number of hours. In fact, the laboratory work in this case was shared by two of us, and results were always available to the clinicians

within ½ to 1 hour of beginning work on each specimen.

Two laboratory conclusions were of special importance.

First, the bleeding state was shown to have the features of an *in vivo* coagulation, and heparinaemia was excluded. There were deficiencies of fibrinogen, antihaemophilic activity (in the sense here adopted) and platelets; fibrinogen was easily replaced but the second and third defied our amateurish attempts at making good.

The other important laboratory decision was to advise against Caesarean section on the evening of 3rd October. The relative risk of operation and normal labour in bleeding disorders is obviously a fundamental problem and is therefore dealt with in the general discussion.

The slow return to a normal platelet count agrees with the findings of Sharp *et al.* (1958).

Discussion

The Risk of Normal Delivery in Bleeding States

Some information is available on which to judge the risks of delivery in various bleeding states.

Coagulation defects. Israëls, Lempert and Gilbertson (1951) described a case of true haemophilia in a woman who underwent labour with a loss of only 120 ml. of blood in the third stage and normal lochial discharge in the early puerperium.

Barnes (1947) treated a series of women with anticoagulants (heparin or coumarins) in the puerperium and found no increase in the lochia.

Thrombocytopenia. Peterson and Larson (1954) collected reports of 65 pregnancies in 47 thrombocytopenic women and added one further case; there was only one maternal death, and of 33 deliveries when the maternal platelet count was below 100,000/mm.^{3} (mean, 35,400/mm.^{3}) there were only 3 in which the third stage of labour was accompanied by abnormal bleeding.

It thus appears that delivery *per vias naturales* is surprisingly safe in the face of a bleeding tendency, and may well be safer than Caesarean section; for, by contrast, operations on haemophiliacs are well known to be extremely hazardous unless the AHG can be raised to a safe level by infusion (Macfarlane *et al.*, 1957).

Signs of Remission in the Bleeding State

It is clearly important to be able to detect the onset of remission in the bleeding state. In the untreated patient recovery will be indicated by a return of the clotting test values towards normal, but in the treated case allowance must be made for the materials infused. The method is to estimate the amount by which the plasma concentration of some component would be expected to rise after a given infusion, and to compare this figure with the observed rise. Fibrinogen is the obvious substance to choose.

In addition, the natural rate of production of the material must be allowed for. Serial estimates of fibrinogen concentration during the recovery phase (Hodgkinson *et al.*, 1954; Ratnoff *et al.*, 1955; Jennison and Walker, 1956; Phillips *et al.*, 1957; Lewis, Leary, Fresh and Ferguson, 1958) give an average rate of restoration of about 20 mg./100 ml. plasma/hour; so that the amount to be added to the increase anticipated from the infusion is a multiple of this value and the time (in hours) elapsing between serial estimations. Clearly, if the observed estimate is well below prediction it indicates a continuation of the destructive process (as in the case reported by Lewis *et al.*, 1958), but when expectation is achieved, it may be inferred that the material is no longer being seriously destroyed. It is of interest that serial fibrinogen estimations during the acute phase showed a fall of some 25 mg./100 ml. plasma/hour in FitzGerald and Jackson's (1956) case; by summation, this clearly represents an actual destruction at the rate of some 50 mg./100 ml./hour. In Jennison and Walker's (1956) case of retained dead foetus, infused fibrinogen disappeared at about 2 mg./100 ml./hour, so that some 2 g. were lost from the circulation over 24 hours.

Management of a Case

We feel that the principles of clinical management should now be along the following lines:

(1) *Adequate investigation.* The nature of the bleeding tendency must be determined so that

deficiencies may be replaced and abnormal anticoagulant substances neutralized.

(2) *Treatment of the bleeding tendency.* Fibrinogen is easy to replace as a purified concentrate; the dose is determined from the estimated total deficiency. Antihaemophilic globulin (Macfarlane *et al.*, 1957) and factor V must generally be supplied as fresh citrated plasma, and platelets as platelet-rich citrated plasma. It is probably better here to avoid sequestrine as the anticoagulant of platelet-rich infusions, since we have observed, in a mild haemophiliac, that the administration of sequestrine plasma leads to a lowering of the plasma concentration of AHG. Whole blood may, of course, also be required to replace blood lost.

Heparinaemia may be treated by injection of protamine sulphate (see above, under description of Test 5) or by toluidine blue, which has been successfully given by mouth (100–150 mg. daily in a nine-year-old boy: Speer *et al.*, 1955). Anticoagulants of the auto-antibody type (e.g., anti-AHG) may be treated with corticoids (Macfarlane *et al.*, 1957, case 8). Various suggestions have been made for the treatment of excessive fibrinolysis. Firkin *et al.* (1957) advised intravenous infusion of human serum albumin in 25 g. doses, to increase the antifibrinolytic activity of the patient's blood. Heuson *et al.* (1958) have recently shown the practicability in a severely shocked patient of administering 300–400 mg. of a crystalline soy bean trypsin inhibitor, which has been shown to neutralize fibrinolysin *in vitro*. Normal blood constituents destroyed in the circulation by the fibrinolysin may, of course, need replacement.

(3) *Termination of the pregnancy.* If the bleeding state develops before there is immediate prospect of delivery, it seems reasonable to induce labour or to accelerate delivery by the natural route: first, because this is the only radical treatment of the cause of bleeding (although, as in the present case, the bleeding tendency may partially recover before delivery); and, secondly, because the repeated infusion of fibrinogen may increase the deposition of fibrin micro-emboli, as in the fatal case described by Graham, Emerson and Anglem (1957), so that the period during which fibrinogen is required should be reduced to a minimum.

Summary

The literature suggests that acute haemorrhagic complications of pregnancy and labour may arise through processes of intravascular coagulation, fibrinolysis or the production of anticoagulant substances of various kinds. There may also be a serious drain on clotting factors in massive retroplacental clot-formation; and protein synthesis might be impaired in the state of shock which often accompanies these conditions.

A simple scheme of laboratory investigation is outlined for determining which processes operate in a given case, and for selecting rational treatment. It is pointed out that the clinical pathologist in consultation with the obstetrician may be able to offer information which will assist the clinical management of these patients.

An illustrative case is described.

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SOME CONTRIBUTIONS TO OBSTETRICS AND GYNAECOLOGY IN LIVERPOOL, 1895–1945*

BY

ARTHUR A. GEMMELL

I WISH to express to the Council of the College my sincere thanks for the honour they have done me by nominating me to give this lecture. Looking over the list of distinguished men who have previously given it I am overawed by the magnitude of the task before me, particularly as I stand before you as a representative of a new generation. All my predecessors have been contemporaries or very near contemporaries of Sir William Fletcher Shaw. The deed of gift states that the lecturer shall be a Senior Fellow of the College and it is difficult for me, who might have been a student of Sir William, to realize that I am now so graded.

It is surely appropriate to mention briefly William Meredith Fletcher Shaw for whom this lecture is named. I had not the privilege of knowing him personally but understand that he was an attractive young man full of energy and fun. He had decided, whilst at school, to become a pottery manufacturer. On leaving school he joined a large firm in Staffordshire. He was certain that war was coming and, so, partly to prepare himself and partly to give a lead to the men in the factory, he joined the Territorial Army more than a year before the actual outbreak of war. He went to France with the 6th Btn. The North Staffordshire Regiment. During the battle of the Falaise gap in July, 1944, he displayed sustained and purposeful courage. He was called upon to obtain a prisoner for identification. He went out accompanied only by a corporal and brought back a prisoner but the identification was not satisfactory. He went out a second time and was reported as missing, wounded and believed prisoner; his corporal being wounded and taken prisoner. William was, in fact, killed and posthumously awarded the Military Cross for his persistent gallantry in action.

World War II has been frequently brought to mind during the preparation of this lecture for so many documents I would have liked to consult have been destroyed—a number of them by enemy action.

Towards the end of the nineteenth century instruction in clinical obstetrics in Liverpool was in a very unsatisfactory state and almost all the students in our medical school went to the Rotunda Hospital to "take their cases". In the city a student lodged with a midwife or near her house but even so there were exasperating delays before he could complete the full number of cases because the midwife often failed to call him. In 1895 the Dean of the Medical Faculty of University College, as it then was, approached the Medical Board of the Lying-In Hospital asking them to take steps to improve the conditions under which the students undertook their practical midwifery. The Faculty added that unless some improvement were forthcoming they would be obliged to approach other hospitals or proceed to the establishment of a rival Lying-In Hospital.

The response of the Medical Board of the Hospital to this was to put forward a series of proposals which included, amongst others, that the students should live together in a house close to the Hospital, provided with a telephone and under the control of the college authorities, and that they should receive instruction from the medical officer of the "district" in which the patient lived—there were 8 of them—between

* The William Meredith Fletcher Shaw Memorial Lecture, 1959, delivered at the Royal College of Obstetricians and Gynaecologists on 16th October, 1959.

the hours of 8 a.m. and 11 p.m., a very leisurely way of doing obstetric clerking.

By 1898 it was obvious that these amended regulations had not fulfilled their purpose. In November, 1898 Henry Briggs was appointed to the Chair of Obstetrics and Gynaecology which had become vacant by the sudden death of Professor John Wallace. Briggs was at once informed by the Dean that he must make the development of the facilities for the teaching of clinical obstetrics his first care. He had a formidable task before him. Vested interests and apathy had interfered with any progress under the 1895 proposals and furthermore Briggs had no obstetric beds, for, under the Regulations of the Lying-In Hospital then in force, an Honorary Medical Officer could only hold his appointment for 10 years. Briggs had been an Honorary Medical Officer from 1884 to 1894. He was convinced that clinical obstetrical teaching could only be properly organized by establishing complete co-operation between University College and the Lying-In Hospital. He worked hard to achieve this and in December, 1898, when my father, J. E. Gemmell, was Secretary of the Hospital's Medical Board, an agreement was signed between the Hospital and the Medical Faculty of the College giving full effect to the arrangements proposed in 1896. The Professor was made a member of the Medical Board of the Hospital with the use of two beds. He undertook the furnishing of the house provided for students in 1896 and installed a married couple as caretakers. Each student paid ten shillings a week for a room and ten to fifteen shillings for board. A resident doctor qualified and with experience in obstetrics—to be called the obstetric assistant—was appointed by the College with the approval of the Medical Board. He was to live in the hostel and be in charge of the students.

The hostel rapidly became a success and very soon the advertisement for the clinical facilities offered at the Rotunda Hospital disappeared from the College magazine. With the success of the hostel however some malicious suggestions were made about the profits which might be made by a professor running a lodging house. The Vice Chancellor, Sir Alfred Dale, was asked to make an investigation and Briggs was completely vindicated for, far from making a profit, he had by 1905 spent £500 out of his own pocket.

The date then of the introduction of proper teaching of clinical obstetrics, with residence provided by the Medical School and Hospital, is 1898. Several of the London teaching hospitals had resident obstetric students before this. Queen Charlotte's Hospital had some arrangement of this kind in the 1790s and opened a residential college for medical students in 1898. The Bristol Royal Infirmary was the first extra-metropolitan institution to provide these facilties. Liverpool and Belfast were equal second in 1898.

Briggs was very much interested and active in teaching. During his tenure of the Chair he built up a magnificent obstetrical and gynaecological museum. Within the museum he included a collection of obstetric forceps which is probably the most complete one in this country. He also left two volumes which may be regarded as a catalogue of this collection and contain much correspondence showing the vast amount of trouble he took to identify the individual instruments.

He also took a good deal of trouble with the instruction of midwives. He founded the Liverpool and District Midwives Association and gave regular courses of lectures to them. His services to the instruction of midwives were recognized by his appointment to the Central Midwives Board in 1912.

The first Midwives Act was passed in 1902 and in 1908 a Departmental Committee was set up to consider the working of that Act. One of the major causes of discontent in the medical profession was the lack of provision for payment for services rendered by doctors in response to a medical aid call by a midwife. Dr. E. W. Hope (1909), M.O.H. of Liverpool, was amongst those who gave evidence. He said that the Act was working harmoniously. In regard to fees for doctors he said there was no difficulty because he had conferred with the members of the medical profession when the Act came into operation and a fee of one guinea had been agreed. The doctor would apply to the patient for this fee and when he was unable to recover it or only recovered some part of it the sum of

one guinea would be made good by the health committee. Dr. Hope believed that this arrangement for the payment of doctors from the very start of the working of the Act was probably the main reason that it worked so well in Liverpool. He also stated that it had been a great help to him to have an organized body of midwives—The Liverpool and District Midwives Association—with which to discuss the working of the Act. It has not been possible to discover in what year Briggs founded the Association but Hope's reference to it suggests that the date must have been prior to 1902.

The Committee amongst their recommendations state that the C.M.B. should lay down that medical help should be summoned whenever a midwife notices symptoms in the mother or child indicating any risk of ophthalmia neonatorum. The Committee had had before it a paper prepared by Dr. Nimmo Walker (1908), a Liverpool oculist, who was an Honorary Surgeon to St. Paul's Eye Hospital and the School for the Indigent Blind. Walker was appalled by the amount of blindness he saw which was due to ophthalmia. His experience taught him that early treatment, very frequent irrigation by day and night and good nutrition, were essential for success. For this purpose a ward containing four beds and four cots was set aside at St. Paul's Eye Hospital in 1907. All cases of newborn babies with a suspicious condition of the eyes were brought to the hospital at once. The midwives, led by their supervisor, co-operated well in securing this. If ophthalmia was diagnosed the baby was admitted at once and an ambulance sent to bring the mother in so that breast feeding might continue. The number of cases of final blindness diminished considerably.

Three outstanding events associated with the Liverpool Maternity Hospital occurred in 1916 in spite of the fact that we were in the throes of World War I. Firstly, a "Rest Home" was opened with 12 beds for "any mother or baby requiring extra nursing and medical attention at a stage of maternity otherwise unprovided for". This, in fact, meant antenatal care, for, from July when the unit was opened to the end of the year, 50 women were admitted in their antenatal period and 23 in their puerperia.

The first antenatal bed in the British Isles was one endowed for this purpose in the Simpson Memorial Hospital in Edinburgh for Dr. Ballantyne. Some beds were specially designated for antenatal patients at St. Thomas's in about 1910 when the Maternity Ward was opened, then in 1916 there followed The Liverpool Maternity Hospital and the Royal Maternity and Women's Hospital in Glasgow. Birmingham also set aside antenatal beds at about this time.

Secondly, the first District Antenatal Clinic in the city was opened. This is believed to be the first clinic of this type in the country. It was the result of consultations between the Medical Board of the Lying-In Hospital and Dr. Hope, the Medical Officer of Health, already mentioned. The premises were provided and maintained by the Health Committee of the Liverpool City Council. The medical staff was appointed on the recommendation of the Lying-In Hospital and the staff of midwives came from the Hospital's District Homes. Eight such clinics were opened almost simultaneously and were such a success that within a year a ninth was added. In the first year's work there were 1,508 antenatal consultations in the hospital's clinic and a total of 1,560 in the district clinics. The first medical officer was Dr. R. A. Hendry.

Thirdly, annual reports on the work of Maternity Units were published a long time ago but with very brief details. For instance there is one in Volume I of *Guy's Hospital Reports* which covers the years 1833–35. However the earliest Registrar's or Clinical Report of something like the form we now know was published by Queen Charlotte's Hospital in 1905; St. Mary's Hospital, Manchester, followed the next year. The Registrar was then Sir William Fletcher Shaw. In the following few years reports appeared from University College Hospital, the Jessop Hospital, Birmingham Maternity Hospital and the London Hospital. The first one from Liverpool was for the year 1916. It was prepared by Dr. R. A. Hendry. The following table (Table I) shows some interesting comparisons between the figures shown in the 1916 report and those in the 1938 report—the last complete year before World War II. It should be pointed out that the hospital of 1916 contained 23 beds whilst that

TABLE I

Liverpool Maternity Hospital—Registrar's Reports

	1916		1938	
	No.	Per cent	No.	Per cent
District	1,086		1,300	
Maternal deaths	2	0·18	0	0
Stillbirths ..	28	2·6	19	1·5
Hospital	570		1,824	
Maternal deaths	9	1·6	9	0·4
Stillbirths ..	74	13·0	131	7·2
Caesarean section ..	25	4·4	210	11·5
Deaths	1	4·0	4	1·9
Forceps	55	9·6	213	11·7
Deaths	3*	5·4	0	0

* All from eclampsia.

of 1938 had 100. It will be noted that in 1916 the proportion of deliveries on the district to those in hospital is roughly 2 to 1 but in 1938 it has become 1 to 1·4. The results under each heading have been improved. The Caesarean section rate has been roughly trebled but the mortality halved. It will be noticed that in 1938 the forceps and Caesarean rates are almost equal whilst in 1916 the forceps rate was more than double that for Caesarean section.

There is an interesting little note in the 1916 Report on the Table for "Induction of labour". This states that "in all cases labour was induced by the introduction of gum elastic bougies, usually three in number". This was a modification of Krause's original single bougie method first described by Briggs in 1893 to the North of England Obstetrical and Gynaecological Society. He believed that the use of three bougies made the induction of labour more certain and shortened the induction-labour interval.

BREECH DELIVERY

Shortly after World War I the profession was deeply concerned by the high stillbirth and neonatal death rate. Under the aegis of the Medical Research Council five centres, of which Liverpool was one, began to study this problem by complete post-mortem examinations of nearly all the stillbirths and neonatal deaths in hospitals. N. B. Capon carried out the work in Liverpool. Papers by him and by Eardley Holland, who was working on the subject in London, appeared in the same number of *The Journal of Obstetrics and Gynaecology of the British Empire* in 1922. Both commented upon the frequency of intracranial haemorrhage especially when a breech delivery resulted in a stillbirth and Capon suggested that this was the result of too rapid delivery of the head.

In 1934, J. W. Burns and C. M. Marshall published their method of dealing (*a*) with the after-coming head and (*b*) with the breech with extended legs. They were able to report the very much improved figures of 2·7 per cent stillbirths in a series of 72 cases. This method is now widely practised and the stillbirth rate in uncomplicated breech deliveries has fallen considerably.

CAESAREAN SECTION

The first Caesarean section in the Liverpool Maternity Hospital was performed by Briggs in 1894. At that time there was great prejudice against the operation as is shown by the following account of a patient who came into the hands of Briggs. "A scolio-rachitic dwarf (Fig. 1) whose internal conjugate diameter was only 2 inches (Fig. 2) and who had been delivered of a dead child with the utmost difficulty, was informed, after a consultation between thirteen members of the staff, that a Caesarean section was essential for the safe delivery of her second child. As she approached her time she was persuaded that Briggs was a rash experimentalist and three of the staff yielded to her plea to deliver the child through the usual passages. A week after this protracted and difficult process the unfortunate patient died of exhaustion and sepsis."

Blair Bell reported (to the North of England Obstetrical and Gynaecological Society in 1920) two cases of lower segment Caesarean section, which he had performed. Unfortunately no details are available. *The Journal of Obstetrics and Gynaecology of the British Empire* had not then resumed publication following World

War I. The Society did not publish transactions independently and, whilst the minute books were in the hands of the Secretary of the Society to enable him to prepare transactions, they, the minute books, were stolen from his car!

St. George Wilson did the first Lower Segment Caesarean section in the Liverpool Maternity Hospital in 1927 and in 1931 he published a series of 50 cases, the majority done at Walton Hospital, with one maternal death. He pointed out that, in contrast with the Classical operation, the lower segment operation could be safely performed after a prolonged trial of labour. In his series the longest interval from onset of labour to performance of the operation was 92 hours.

In 1939 Marshall published his very complete work on Caesarean section—the lower segment operation. He analyzed his results in great detail. It must, however, suffice here to state that by 1939 he had undertaken the operation on 246 occasions without a death. He had used the lower segment operation in placenta praevia for 43 patients and was convinced that the advantages of the lower segment approach, when combined with intelligent planning of the actual uterine incision, far outweighed the disadvantages of some increase in blood loss.

General Conditions and Pregnancy

The study of General Conditions and Pregnancy will always be associated, in Liverpool at least, with the name of Leyland Robinson. He produced three important papers in this sphere within three years. The first of these appeared in 1930 and was entitled "The Old Multipara". His paper was one of the earliest, if not the earliest, on this subject. The risks associated with increasing age and parity as pointed out by him are now well recognized and there has been no need for material additions or subtractions since he enunciated them.

This was followed in 1931 by an article on "The Influence of Childbearing upon Pulmonary Tuberculosis". The material for this paper was obtained by means of a questionnaire which was widely circulated and produced 200 replies. His analysis and marshalling of the material clearly reflects his methodical and critical mind. He found that there was a very limited field for therapeutic abortion in the care of these cases and favoured labour units in Sanatoria so that there should be continuous care in pregnancy, labour and the puerperium under the best possible conditions.

The third paper in 1933 was called "The Effect of Reproduction upon Insanity". It again was based upon the replies to a questionnaire. The points for and against therapeutic abortion and sterilization are very fully described and he concluded that "There is no scientific evidence to show that the introduction of legalized abortion and sterilization would produce any results commensurate with the practical difficulties".

Anaesthesia

In parenthesis it is perhaps interesting that both Briggs and J. E. Gemmell were Edinburgh graduates and that the first hospital appointment in Liverpool of each was that of "Chloroformist" to the Royal Infirmary. The appointment of Briggs in 1883 was the first of its kind in Liverpool.

In 1927 St. George Wilson was the first to present to the North of England Obstetrical and Gynaecological Society a carefully recorded series of cases of Scopolamine-Omnopon narcosis or "Twilight Sleep". He followed the lines which had been laid down by the Royal Society of Medicine in 1917. A main precaution was to exclude external stimuli and I well remember the basement room in the Rest Home, prepared as for a domiciliary confinement, in which he conducted these labours. His findings corresponded with those reported to the Section of Obstetrics and Gynaecology of the Royal Society of Medicine. The method required the constant and unremitting attention of the doctor, uterine contractions were reduced in force and frequency, there was an increased forceps rate and a tendency to third stage bleeding. The babies showed oligopnoea but responded quite rapidly to a warm bath. The method which had never found much favour in Liverpool was virtually given up completely following this paper.

In 1933 the Medical Board of the Liverpool Maternity Hospital asked Dr. R. J. Minnitt,

THE RACHITIC DWARF

Standing by the side of the Matron (Miss Gosling) of the Lying-in Hospital, Liverpool, October, 1889.

FIG. 1

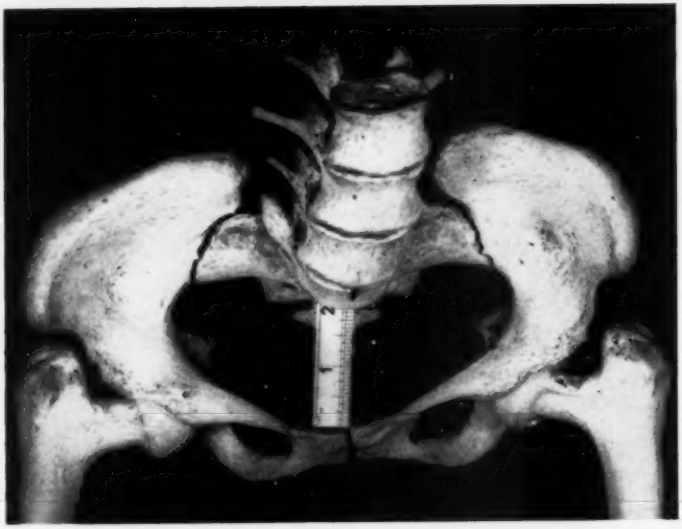

FIG. 2

The actual pelvis of the dwarf showing the true conjugate.

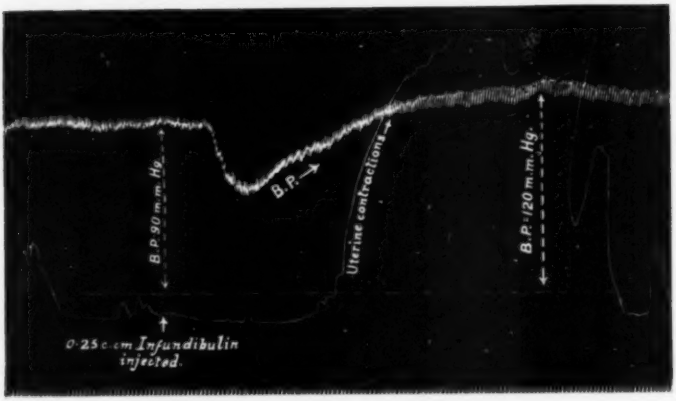

FIG. 3

Kymograph-tracing showing the pressor effect of an intravenous injection of infundibulin on the blood pressure and uterine contractions of a pregnant cat. It will be observed that there is a preliminary fall in the arterial tension, and that the heart beat is slower, but increased in force, after the injection.

their Consulting Anaesthetist, to suggest a possible scheme for research on anaesthesia in labour. The agent used was to alleviate the pains of labour without interfering with uterine action. Further, the method was to be one applicable to general practice, and one which the doctor could safely leave to the midwife in his absence.

Minnitt had been impressed with the use of nitrous oxide in dental extractions and worked on the production of an apparatus which would give an intermittent flow of gas and air. The apparatus was first put into use in the Liverpool Maternity Hospital in September, 1933. The first paper on it was delivered by Minnitt in the Liverpool Medical Institution in February, 1934. Within a few months objections were raised because midwives had been using the method without medical supervision. The Central Midwives Board felt themselves compelled to insist upon direct medical supervision so the development of this method was held up. In the autumn of 1934 a Committee was set up by this College to investigate anaesthetics in labour, generously financed by the National Birthday Trust. Many agents were investigated in thirty-six hospitals throughout the British Isles. When the report was issued in January, 1936, gas and air received warm commendation which resulted in the Central Midwives Board issuing regulations governing its administration by midwives with a recognized apparatus.

Marshall (1939) in his book already mentioned emphasizes the virtues of local anaesthesia for Caesarean section especially in cases of heart disease, bronchitis and toxaemia. He reported that in a 6-year period at the Liverpool Maternity Hospital 6 deaths had occurred in elective Caesarean section for which a general anaesthetic was, at least, mainly responsible, that is, almost one-third of the total mortality in the period could be attributed to this cause.

Myomectomy

Towards the end of the nineteenth century the operation of myomectomy had largely fallen into disuse. William Alexander of the Royal Southern Hospital, Liverpool, however, decided to revive it. Alexander's name was already associated with an extraperitoneal operation for shortening of the round ligaments. This operation was devised in the period preceding the era delineated by my title and is mentioned now only because Alexander read a paper on it to an early meeting of the newly-established British Gynaecological Society in 1885. This paper was published in the first volume of the *British Gynaecological Journal*.

The paper on myomectomy was presented to the Liverpool Medical Institution and to the British Gynaecological Society in 1898. Eleven cases were recorded with one death which was attributed to the operation—a mortality of 9 per cent (there were two other deaths—one, a year later, from "cancer of the liver", the other, some three weeks after the operation, from a cerebral condition which formed part of the indication for the operation). This is a remarkably low mortality for Bonney has told us that the mortality from hysterectomy at that time ranged between 12 and 20 per cent.

Alexander favoured a single anterior midline incision into the uterus and reaching all the fibroids through this. He was worried about oozing in the uterine wound and overcame this by packing the cavity he had created with iodoform gauze which was removed a foot at a time commencing 48 hours after the operation.

The discussion, also reported in the *British Gynaecological Journal*, makes depressing reading. Many of the well-known figures of the day took part in the discussion. None was favourable to the operation and most decried it because it had been abandoned on the Continent.

However, the operation was not entirely abandoned and a few case histories and a paper appeared up to 1914. Leith Murray, always a strong protagonist of conservative gynaecology, began to undertake this operation when he returned from war service. He published his first paper on it in 1926 and recorded 60 myomectomies involving one or more incisions into the uterine muscle, all in non-pregnant women.

There were no deaths in this series. None of the patients who were single at the time of the operation had married but 7 (or 20·6 per cent) of the 34 married women operated on not less than a year previously had had 9 children

following it and 2 others had had miscarriages. In 1930 Leith Murray's second paper was published. The total number of non-pregnant women who had now been operated upon, including the early series, was 137 with 1 death —a mortality rate of 0·73 per cent. During the same period he had undertaken 535 hysterectomies for fibroids in non-pregnant women with 8 deaths—a mortality rate of 1·5 per cent. At the time of the earlier paper he had been doing one myomectomy to 3·73 hysterectomies whereas from June, 1925 to the end of 1929 the relationship was 1 to 2·8.

In the total of 84 cases where pregnancy was reasonably possible it was found to have occurred in 27·3 per cent.

Operative Technique

Blair Bell published in 1918 a striking advance in operative technique which has been largely overlooked possibly because it was entitled "A method of dealing with the divided ureters". Actually this paper describes what is now called anterior exenteration and includes a description of the formation of an isolated ileal loop into which the ureters were transplanted. The urologists never seem to quote this paper.

Research

Thinking of research work in this period one's mind turns instinctively to Blair Bell, but we must not overlook the contributions made by Leith Murray especially before World War I. A whole book could be written about Blair Bell's work and a sizeable monograph about that of Leith Murray so that I can here only give some examples for both of them.

Blair Bell's fertile brain and infinite capacity for work covered a very wide range of subjects. He was an early worker in the physiology of the female genital organs and in their development. He produced a number of articles on the endocrines especially the thyroid and pituitary whilst in his later years he both worked hard himself and guided a distinguished team in the problems of cancer. He wrote two whole books on his earlier researches—*The Sex Complex* (1916) and *The Pituitary Gland* (1919).

In the clinical application of research I hope he will be especially remembered for his introduction of pituitrin or as he called it, "infundibulin", into therapeutics. In a paper published in 1909(a) part of it was devoted to substances which promoted uterine contractions. He investigated seven substances of which one was pituitary extract. Blair Bell knew that Sir Henry Dale had shown that this extract produced uterine contractions in 1906 and it was Sir Henry who prepared the extracts for this trial. Bell found that infundibulin was the most powerful stimulator of contractions of the pregnant uterus. Here is his own actual slide (Fig. 3) showing tracings of the effect on uterine contractions and the blood pressure in a pregnant cat. He was so convinced by the observations he made in these experiments that he decided on clinical trials and through the agency of Sir Henry Dale, Messrs. Burroughs, Wellcome & Co., provided a considerable supply of the extract for clinical use. The uses for which it was prescribed were to raise blood pressure especially in patients suffering from shock, to stimulate contractions in paralyzed and distended intestine and to stimulate or enhance contractions in the parturient or post-partum uterus. In 1909(b) he published a paper in which clinical results as observed by his colleagues were presented. Each of the three indications was strongly supported. Blair Bell sought for and valued the opinion of independent observers. The following extract from this paper is amusing. Some of the material had been put in the hands of Dr. Hendry, the obstetric assistant who had sent the house surgeon to a case of post-partum haemorrhage on the district. Hendry reports "the house surgeon said to me on his return, 'What do they need anything better than ergot for? The lot I injected acted like a charm.' I knew, however, that there was no ergot in the bag, so I asked him to show me the box he got it from, whereupon he produced the infundibular extract."

The work to which Blair Bell chiefly devoted himself was the study of cancer. Please note "study of cancer" not "lead treatment of cancer". Blair Bell claimed that there was close similarity between chorionic epithelium and the malignant somatic cell. He stated, in an address to the Abernethian Society of St. Bartholomew's

Hospital (1927), that his research group had "shown what cancer is and how it is caused" and went on "we claim much less for treatment of cancer by lead—the only part of our work that has attracted attention! As I have often said we regard the action of lead on malignant cells only as confirmatory (toxicologically) of our views concerning the similarity between the chorionic epithelium and the malignant somatic cell." Blair Bell gathered round himself a team of well-known scientists and clinicians, all on the staff of the University of Liverpool, and formed them into a group—the Liverpool Medical Research Organization—of which he was the inspired and inspiring leader. In the Department of Obstetrics and Gynaecology at Liverpool there are two bound volumes containing reprints of just over seventy articles prepared by this Organization between the years 1922 and 1933. These papers cover a vast amount of work on the chemical composition of cells, cell metabolism and the action of lead upon cells; collectively a notable contribution to cellular physiology.

In 1910 Leith Murray read a paper on "the Haemolytic Lipoids of Degenerating Fibroids with special reference to Red Degeneration" to the North of England Obstetrical and Gynaecological Society. Not only did he describe fully the histological appearances of red fibroids but he also recovered some lipoid from them and examined certain of its properties. Fairly large quantities of fat were found in the degenerated red areas as had indeed been noted by Fletcher Shaw a year earlier. Correlating the Sudan III staining with the lipoid content of the tumour he concluded that, where there was little staining with this agent but still a considerable lipoid content, it was of a soapy nature rather than fatty. The vessels of the tumour showed disorganization in their walls. The lipoid was proved to be haemolytic by its action on suspensions of pooled corpuscles in saline. It was also noted that if excess of lipoid were present a brownish tint appeared. From this he deduced that, if *in situ* the process continued, it would lead to the substitution of the red colour by a greyish brown tint. Murray considered that the focus of haemolysis lay within the degenerated vessel itself.

Although it is not mentioned in the article Leith Murray always taught that the "red" fibroid, the "wash leather" fibroid and the calcified fibroid were stages in the same process and that that sequence was of the same order as that well recognized in general pathology—fatty change—saponification—calcification.

Just as Blair Bell's work on cancer did not lead to the finding of a cancer cure so Leith Murray's arresting paper of 1913 on the Immunology of Pregnancy has so far led to no conclusion but it is noteworthy that interest in this subject is being revived today. Murray's paper is, at least, intriguing but I am informed that some of his experiments would not be accepted in the light of modern knowledge as providing the evidence he attached to them. However, we now know the antigen-antibody nature of haemolytic disease of the newborn so why should not a similar reaction take place in the opposite direction?

General Advances

Whilst our predecessors were engaged in the improvement in practice of our own branch of medicine they did not stand aside from general advances that were taking place but took an active part in furthering them.

Radium

By 1928 it was widely recognized that radium was an important element in the treatment of cancer. Various centres in this country had supplies of it but Liverpool had only 137 mg. at the Royal Infirmary. A group of surgeons decided to press for a fund to supply Liverpool with an adequate amount. Prominent in this group were Leith Murray and Miss Frances Ivens. A special word is called for about Miss Ivens. She was appointed to the Consultant Staff of the Liverpool Stanley Hospital in 1906 as Honorary Medical Officer for Women's Diseases. It is traditionally believed in Liverpool that she was the first lady doctor to be appointed to a consultant post outside London. She served with the Scottish Women's Hospital in France in World War I. This hospital was eventually taken over by the French Army and Miss Ivens was awarded the Legion of Honour.

In 1929 a town's meeting was held at the Town Hall which decided to establish a fund for the purchase of radium.

The money must have been collected rapidly for the first patient suffering from carcinoma of the cervix to be treated by radium in the Women's Hospital was admitted on 20th June, 1929. The dosage and time factors were those of the standard Stockholm technique. Unfortunately there is no "follow-up" record for this patient.

Blood Transfusion

The history of Blood Transfusion, a procedure we now use so freely, is a fascinating one. It fell into disrepute towards the end of the eighteenth century because of lack of knowledge of the physiology of the blood. In the later part of the nineteenth century a number of people tried to improve matters. Notable amongst them were obstetricians who were disturbed by the bad results of current methods in post-partum haemorrhage.

In Liverpool a noteworthy contribution was made by Higginson although at an earlier date than the period covered by this lecture. Higginson was a Surgeon to the Southern Hospital, Liverpool, and is, of course, best remembered for the invention of his enema syringe which he described in 1847. However in 1871 he published a paper on thirteen patients whom he had transfused. Ten of these patients were obstetrical—four cases of post-partum haemorrhage, three of placenta praevia, one adherent placenta, one abortion and one "Fallopian foetation". In four cases he reported a successful outcome—three in post-partum haemorrhage and the one abortion.

The procedure fell into disuse but the experiences of World War I brought it to notice again. There was however no organization of donors or the means of calling them in an emergency. The medical boards of the Liverpool Maternity Hospital and the Royal Infirmary recognized the need for such an organization and took the leading part in working for its establishment. Through their efforts the Merseyside Blood Transfusion Service was set up in 1930. The organization, clerical work and a day and night telephone service were undertaken by the Liverpool University Settlement and the British Red Cross Society accepted initial responsibility for the expense. At the outset donors were chiefly recruited from the Rover Scouts.

In conclusion I hope that my colleagues in Liverpool will feel that this summary has not overlooked any vitally important contribution to the advancement of Obstetrics and Gynaecology by our medical school in the first half of this century. I have purposely omitted reference to the work of those still actively engaged in practice with the one exception of Dr. Minnitt.

My thanks are due to many who have helped me in the collection of material and in particular to the Department of Obstetrics and Gynaecology of the University of Liverpool.

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URINARY INFECTION AFTER COLPORRHAPHY: ITS INCIDENCE, CAUSATION AND PREVENTION

BY

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IT is surprising that so little attention has been paid to the incidence and prevention of urinary infection following colporrhaphy. In the multiplicity of operations described for the cure of urinary symptoms in the female those writers who mention the problem comment briefly that the patient should be dismissed with a sterile urine.

Our interest in this subject was stimulated by an increasing awareness of the part played by urinary infection in the residual symptomatology after colporrhaphy. When we investigated what was, at that time, our standard post-operative practice we were appalled by the incidence of urinary infection revealed. Alteration of our post-operative technique produced some diminution in the incidence of urinary infection but significant improvement did not occur until the introduction of our present combined aseptic and antiseptic technique. We present the results of 176 cases, divided into three series according to the clinical methods employed.

MATERIAL AND METHODS

Catheter specimens of urine were collected at carefully specified times which will be separately detailed for each of the three series and these specimens were examined within two hours of collection. The centrifuged deposit of each specimen was examined by microscopy of a Gram-stained film and by culturing on blood-agar and MacConkey plates for eighteen hours. Strains of *Staphylococcus aureus*, *Streptococcus faecalis* and *Proteus* spp. were identified in the usual way. Most strains of *Staph. aureus* were phage-typed. Gram-negative bacilli which fermented lactose were grouped as coliform bacilli. Evans' "Sentest" tablets were employed to assess the antibiotic sensitivities. A specimen of urine was considered to be infected when pus cells and organisms were present on the direct film and a positive culture was obtained. A light growth of organisms in the absence of pus cells was disregarded.

When an in-dwelling catheter was employed, this was inserted in the theatre at the end of the operation. Intermittent catheterization was at first done as follows. A boiled glass catheter was introduced after the urethral meatus had been swabbed with 1/1,000 solution of chlorhexidine. The hands were scrubbed but not dried. The instillation of chlorhexidine was carried out through a small glass funnel attached to the end of the catheter by means of a short piece of rubber tubing. The funnel and tubing were separately boiled. We have discarded the use of a soft rubber catheter as it cannot be introduced without considerable handling by the attendant who in a busy ward cannot find the time to decontaminate his hands effectively between each patient.

We have now modified the catheterization technique as follows. The catheter, tubing and funnel are autoclaved. Preliminary scrubbing of the hands is not considered necessary but a dry-hand technique is essential. The hands are washed with soap and water and carefully dried on a clean freshly-laundered towel. Then, with the labia separated, the urethral meatus is swabbed with a solution of 1/1,000 chlorhexidine. The catheter, held one inch from the open end is introduced, the bladder emptied, the funnel attached and chlorhexidine instilled. In the event of the catheter not being directly introduced at the first attempt it is discarded and a fresh one employed.

Results

Series I

In this series, which formed the control, the pre-existing methods were used.

A catheter specimen of urine was taken in the theatre before operation and at the end of the operation an indwelling rubber catheter was inserted and left *in situ* for 48 hours. This catheter was spigotted and released four-hourly. Immediately before removal of the catheter a further specimen of urine was taken for examination. After removing the indwelling catheter the patients were catheterized night and morning, after micturition, until the amount of residual urine fell to two ounces or less. Obviously, patients who were unable to urinate required catheterization more frequently. The last specimen of residual urine was submitted to bacteriological examination as was a further catheter specimen taken after treatment of any urinary infection which at that time was considered to merit treatment.

Forty-nine patients comprised this first series but one of these was found to have a urinary infection at the time of operation, leaving forty-eight to be considered. When the indwelling catheter was withdrawn, some 48 hours later, 34 of the 48 (71 per cent) already had a urinary infection at this early stage. Catheterization to measure residual urine was carried out on an average of 9 times on each patient and the average duration of persistence of residual urine was 6·5 days. When this final residual specimen was examined 42 (87·5 per cent) were infected. The overall incidence of urinary infection, i.e., the number of patients infected at any time in the post-operative period was 92·5 per cent (Table V). Despite the extensive use of sulphonamides and antibiotics as shown in Table II, 32 of the 48 patients (66·6 per cent) were dismissed with a urinary infection. The organisms responsible for the infections at the various times are shown in Table I.

The average stay in hospital after operation was 13·5 days.

Table I

Organisms Found in Infected Urines of Patients in Series I

	At Operation	At 48 Hours	At Last Residual Catheterization	At Dismissal
No. of patients not infected	48	14	6	16
No of patients with:				
Coliforms	1	11	25	16
Coagulase-positive staphylococci ..	0	11	5	7
Coagulase-negative staphylococci ..	0	4	2	1
Mixed infection	0	5	9	7
Strep. faecalis	0	2	0	0
Proteus spp.	0	1	1	1

Series I.—The patients of Series I had an indwelling catheter in the bladder for 48 hours after operation. Thereafter residual urine was estimated night and morning until the volume was two ounces or less.

Series II

In an effort to reduce this high incidence of infection, the use of the indwelling catheter was discontinued as was the serial investigation of the amount of residual urine. The patients were encouraged to void spontaneously by the more lavish use of analgesics and by allowing them up to a bedside commode after the first day.

Catheter specimens of urine were obtained for examination:

(1) In the theatre before operation.

(2) At 48 hours, after operation, but only if the patient required catheterization, and not routinely.

(3) At a check of the residual urine made on the seventh morning. This, if the residual urine was over 4 ounces, was repeated on the eleventh morning, and thereafter at four-day intervals until the residual urine was less than 4 ounces.

(4) When a catheter specimen was examined as a test of cure following treatment of infection.

Eighty-one patients comprised Series II, but of these 5 were infected at the time of operation, leaving 76 for consideration (Table III).

Thirty-four patients required catheterization at 48 hours and, of these, only 8 (25 per cent) were infected. When the specimens of residual urine were examined on the seventh day, 49 of the 76 patients (64 per cent) either had been treated for or currently had a urinary infection and the overall figures for the series showed that 58 patients (70 per cent) had at some time developed a urinary infection post-operatively. The drugs used in the hope of sterilizing the urine are shown in Table II. In some cases more than one course of treatment was required. The infecting organisms present are shown in Table III.

It is particularly noteworthy that patients whose urine remained sterile throughout were catheterized on an average only 3·5 times, whereas in those whose urine was infected this figure rose to 13·5.

As serial estimations of the residual urine were not being carried out it was not possible to show its persistence accurately. However, in the

TABLE II

Substances Used, Per 100 Patients, in Each of the Three Series, in an Effort to Attain Urinary Sterility

	Series I	Series II	Series III
	Per cent	Per cent	Per cent
Treated	52	64·5	13·5
Infected on dismissal ..	66·6	17	0

Substance Used	No. of Times Used/100 Patients		
Sulphonamides ..	25	4	0
Penicillin	2	4	0
Streptomycin	15	18	0
Chloramphenicol ..	6	38	6
Tetracyclines	12	18	0
Nitro-furantoin ..	0	1	0
Mandelamine	0	0	1

TABLE III

Organisms Found in Infected Urines of Patients in Series II

	At Operation	At 48 Hours	At 7 Days	At Dismissal
No. of patients not infected	76	26	30	64
No. of patients with:				
Coliforms	4	6	26	5
Coagulase-positive staphylococci ..	0	0	8	3
Coagulase-negative staphylococci ..	0	0	1	0
Mixed infection	0	2	4	1
Strep. faecalis	0	0	1	0
Proteus spp.	1	0	6	3

Series II.—The patients of Series II were catheterized as and when required. The residual urine was estimated on the seventh day and, if of greater volume than four ounces, at four-day intervals thereafter.

infected cases, 17 had a residual urine of less than two ounces on the seventh day, and 36 had a larger quantity. In the 23 patients whose urine was not infected at any time, 16 had a residual urine of less than two ounces on the seventh day and only 7 had a greater volume.

Due to the increased resolve to ensure a sterile urine before dismissal from hospital the average duration of post-operative stay rose to 16·3 days but despite this, 12 patients (15·8 per cent) were dismissed with a urinary infection.

The results in this second series of cases were better than the first series but were still by no means satisfactory. Our attention now turned to some means by which these results could be improved. It has hitherto been universally accepted that the three main causes of post-operative urinary infection are post-operative residual urine, operative trauma, and a low haemoglobin level (Malpas, 1958).

Of these causes, a low haemoglobin level should not apply in what is after all an elective procedure and any excess blood loss at operation can be rapidly made good by transfusion. It is a general surgical principle to reduce operative trauma to the minimum and this cause should certainly not be important in any large group of patients. There remains therefore the question of residual urine. It is our contention that residual urine does not become infected spontaneously but is infected by catheterization. That this may be carried out with full aseptic precautions and still result in urinary infection is shown by the work of Guze and Beeson (1956) who isolated *Escherichia coli* from the mid-urethra in 5 of 13 women examined and in whom no instrumentation had been previously carried out. This suggests how easily organisms can be introduced into the bladder even by a single catheterization despite allegedly impeccable technique.

It seemed, therefore, that catheterization must be restricted to the minimum and either urinary infections treated as they arose or some method of prophylaxis employed. The use of the sulphonamides has proved disappointing. Durham *et al.* (1954) have shown that the incidence of infection fell little by such means and sulphonamide sensitive organisms were replaced as pathogens by others which were sulphonamide resistant. This has also been demonstrated by Garrod *et al.* (1954). The common infecting organisms in the present investigation were sensitive only to chloramphenicol and tetracyclines and these drugs were not considered suitable for prophylactic use.

There remained however the possibility of preventing urinary infection, if it were in fact inoculated by the catheter. This necessitated rendering the urine in the bladder either bactericidal or at least bacteriostatic. This could best be done by instilling an antiseptic into the bladder. Chlorhexidine (Hibitane) was selected as it had previously been used as a cystoscopic medium and for bladder irrigation (Beeuwkes and de Vries, 1956). It was known to be of low cytotoxicity (McLeod and McLeod, 1959) and is bactericidal in high dilution to the common urinary pathogens (Table IV). The results obtained with this technique are given in Series III.

Series III

Catheter specimens of urine were taken for examination at the same time as in Series II. After each catheterization, except for the pre-operative one in theatre, two ounces of a sterile solution of chlorhexidine were instilled into the bladder. Examination of a specimen of urine at 48 hours was discontinued as it would contain a high concentration of chlorhexidine.

TABLE IV

In Vitro *Determinations of the Concentrations of Chlorhexidine Required for Bacteriostatic and Bactericidal Effects*

Organism	Concentration for	
	Bacteriostatic Effect	Bactericidal Effect (99·99 per cent (kill))
Coliform	1 in 100,000	1 in 50,000
Staph. aureus ..	1 in 1,000,000	1 in 40,000
Strep. faecalis ..	1 in 1,000,000	1 in 20,000
Proteus vulgaris ..	1 in 200,000	1 in 50,000

In vivo the concentration attainable in the bladder ranged from 1 in 5,000 to 1 in 50,000 according to the fluid contents (2–20 ounces).

Initially a sterile solution of 1:1,000 chlorhexidine prepared from the concentrate as supplied by the manufacturers was employed. Unfortunately this produced haematuria in four of the first five cases, the last so gross that the "urine" clotted and the patient required transfusion. In the mistaken idea that the haematuria was due to too high a concentration of chlorhexidine this was reduced to 1 in 5,000. Haematuria still occurred but not to such a gross degree.

The concentrate, however, not only contains chlorhexidine diacetate and a vegetable dye (Edicol Supra Carmoisine), but also an anti-rusting compound (Sorbitol) and a wetting agent. We have since been supplied with the pharmacology of the wetting agent (Lissapol NX) and this would seem to be responsible for the haematuria. The additives were discarded and thereafter a 1 in 5,000 sterile solution of chlorhexidine diacetate prepared from the dry powder was employed. Haematuria has not recurred.

This series comprises 53 patients excluding those in whom solutions prepared from the concentrate were employed. Of these, one was infected at the time of operation leaving an effective series of 52 patients.

When the seventh day post-operative residual specimen was examined 6 (11·5 per cent) were infected and only one other patient developed a urinary infection, an overall incidence of 13·5 per cent. The 7 patients who became infected could be divided into two groups. In the first group of four, catheterization had been employed 6, 13, 16 and 27 times and the organisms responsible were coliform on 3 occasions and *Proteus* spp. on one. In the other 3 patients who became infected, each catheterized 3 times, the operation specimen was sterile but the next catheter specimen taken on the seventh day was infected. This suggests that infection was introduced by the pre-operative catheterization and it is of interest that this initial catheterization was never followed by the instillation of chlorhexidine. We now instil chlorhexidine routinely at the pre-operative catheterization without any apparent increase in the risk of bladder trauma. The infecting organisms were coliform on two occasions and *Proteus* spp. on one.

In the patients who were not infected the average number of catheterizations was 7·5 with a range of 2 to 22. In the non-infected group a residual urine on the seventh day of two ounces or less was found in 29 cases and of over 2 ounces in 16. The comparable figures for the infected patients were 4 and 3. The preparations used in the hope of sterilizing the urine in the infected cases are shown in Table II. No patient was dismissed with an infected urine and the duration of stay in hospital post-operatively fell to 12·5 days. Table V summarizes and compares the findings of the three series.

Discussion

The incidence of urinary infection disclosed in the first series of cases seems very high but

Table V

Incidence of Urinary Infection in 176 Patients After Colporrhaphy

	Series I	Series II	Series III
Total number of patients under consideration	48	76	52
Percentage incidence of infection:			
7 days after operation	87·5	64·5	11·5
Overall	92·5	70·0	13·5
On dismissal from hospital	66·6	15·8	0
Mean post-operative stay in hospital (days)	13·5	16·3	12·5

See particulars in Tables I and III for details of treatment of patients in Series I and II.

Patients in Series III were catheterized as and when required and after each catheterization two ounces of a 1 in 5,000 solution of chlorhexidine diacetate instilled into the bladder.

agrees almost exactly with the 92·6 per cent found by Durham *et al.* (1954) in their series and is only slightly higher than the 88 per cent which these workers found with the use of prophylactic sulphonamides. Champ (1955), in a series of 150 cases of plastic vaginal surgery, found an incidence of post-operative infection of 68 per cent.

These figures are all for a series of patients where the indwelling catheter was used. The lower figure reported by Champ could be accounted for by different criteria of urinary infection. In Series II, where intermittent catheterization was employed, an incidence of urinary infection of 70 per cent was found and we consider that these figures of approximately 90 per cent and 70 per cent are figures of the order that may be expected after colporrhaphy depending upon the type of catheterization employed.

Catheterization

The problem of urinary retention after vaginal plastic operations is one which has not yet been satisfactorily solved and it must be accepted that a large proportion of these patients will require catheterization in some form.

In many of the procedures described, the post-operative use of an indwelling catheter is advocated for a period of time ranging from 2 days upwards (Shaw, 1949; Bailey, 1954, 1956; Pacey, 1949; Marshall *et al.*, 1948).

In Series I, in which the catheter was left in position for 48 hours, the incidence of infection was 71 per cent and presumably an even higher incidence would have resulted with a longer period of catheterization. Although a reduced incidence of urinary infection might result from the introduction of a closed aseptic system of drainage as advocated by Pyrah *et al.* (1955) we contend that the use of the indwelling catheter should be abandoned because it is an almost constant source of ascending infection. Where no indwelling catheter is employed many patients will void spontaneously and this may be further encouraged by the use of the bedside commode. For those who do require catheterization intermittent use of the instrument is less likely to be followed by infection as shown in Series II. This reduction, although significant, still leaves too high an infection rate which requires systemic therapy.

As the figures in Series III demonstrate, it is possible to effect a marked reduction in post-colporrhaphy urinary infection by the use of intermittent catheterization with the instillation of a solution of chlorhexidine as described. A further reduction could almost certainly be obtained by the instillation of chlorhexidine with the pre-operative catheterization. This is now our standard practice.

Residual Urine

Much has been written on this subject. The standard teaching in most centres is to regard residual urine as more dangerous than repeated catheterization. Donald in *British Obstetric and Gynaecological Practice* (1958) in discussion of the post-operative bladder states ". . . she must be catheterized at once, if necessary repeatedly, until measures of residual urine have decreased to less than 2 ounces. Failure to do so invites inevitably urinary sepsis compared with which the risks of infection due to catheter-passing are negligible." Jeffcoate (1957) states, "It is better to catheterize too soon than too late and too often than too seldom. Cystitis is more likely to result from residual urine than from the passage of a boiled rubber catheter."

With this view we have come to disagree entirely. In Series I, where serial estimations of the residual urine were carried out, the overall incidence of urinary infection was 92·5 per cent. We believe this residual urine is only dangerous should it become infected and that this infection is introduced by the catheter. This is borne out by comparing the figures in Series II and Series III. The suggestion that haematogenous infection occurs from the bowel is not supported by our figures since, for the most part, cases which were not catheterized did not become infected.

Infecting Organisms

It will be seen that in Series I *Staph. aureus* was a frequent pathogen. This organism was phage-typed and proved usually to be similar to the known ward *Staph. aureus* which was causing intermittent abdominal wound infections. Staphylococcal infection was also common in the second series but these could

TABLE VI

To Show Persistence of Different Infecting Organisms as Revealed by Follow-up Examination

Infecting Organisms	No. of Patients Infected at Dismissal and Followed Up	Urinary Status at Follow-up	
		Sterile	Still Infected
Coliform	20	8	12
Staphylococcus	8	7	1 (Proteus)
Mixed	8	3	5
Proteus	3	2	1

not be phage-typed and it would appear that in Series I the infection was spread by fomites, whereas in Series II it is more likely that these organisms were either introduced from the patient's vulva or from the attendant carrying out the catheterization. It is significant that staphylococcal infection did not appear in Series III where chlorhexidine was being instilled. We suggest therefore that this instillation of chlorhexidine after catheterization will provide a method of control of this type of infection which has recently merited and received considerable attention (Schwabacher, 1958; Payne, 1959). *Strep. faecalis*, although not a common organism in the present investigation, has also disappeared completely from Series III and as a result the mixed infections have disappeared.

There remain the coliform and *Proteus* spp. infections and these have been considerably reduced. *Pseudomonas pyocyanea* has not been found in any of the three series.

It is interesting to note the persistence of these urinary infections. In all, 44 patients were dismissed with a positive urine. The findings at follow-up examination are given in Table VI. These follow-up examinations were conducted a minimum of six weeks after operation and in the majority of the cases reported the findings are approximately 12 weeks after operation.

Staphylococcal urinary infection present on dismissal was never found to be present at follow-up examination. In all but one case, the urine was sterile, the exception being a proteus infection. In contrast to this, of the 20 cases of coliform urinary infection present at dismissal, 12 had persisted, in one of the cases for a period of 8 months. Surprisingly, of the 3 proteus infections where the follow-up is known, 2 disappeared spontaneously.

It would seem from the foregoing that urinary infection in the female may and frequently does follow catheterization, and that this catheterization implants organisms directly into the bladder, where they flourish under almost ideal cultural conditions. As a means of prevention we suggest that each and every catheterization in the female should be followed by the instillation of a sterile solution of chlorhexidine. This procedure has been shown to be harmless and to reduce the incidence of urinary infection. This in turn reduces the necessity for treatment; finally it reduces the time spent as a patient in hospital.

SUMMARY

(1) The incidence of urinary infection after colporrhaphy was found to be 92·5 per cent in patients where an indwelling catheter was used post-operatively.

(2) With intermittent catheterization this incidence was reduced to 70 per cent.

(3) The instillation of a sterile solution of chlorhexidine diacetate 1 in 5,000 after catheterization reduced the incidence of urinary infection to 13·5 per cent.

(4) This technique is suggested after every catheterization of the female bladder.

(5) The theory that residual urine is the cause of post-operative infection is thought to be erroneous.

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CANCER OF THE FEMALE PELVIS

BY

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WHEN invited by Professor Loewenthal to address you on the subject of Pelvic Cancer in the Female, I felt that some of the younger generation with more time and energy should do so, but on second thoughts, I realized that I am the only living gynaecologist at Royal Prince Alfred Hospital able to review the changing treatments of this female disease over the past 55 years, and consented to be here today.

I wish first to give the historical facts briefly and then record the latest departmental statistics on the subject. You will then get a clear picture of the commendable progress made over the years by the gynaecologists of this hospital in the treatment of female pelvic cancer.

You may or may not know that prior to the announcement by Professor Wertheim of Vienna in 1898 that he had saved cases of uterine cancer by his abdominal radical hysterectomy plus lymphadenectomy, all sufferers were doomed to die a painful and lingering death. My first personal contact with this dreadful problem was in 1907 when, as a resident medical officer, I saw many of these lost causes in the casualty and out-patient departments. When my turn came for gynaecological resident medical officer service, Drs. Foreman and Thring were treating some of these cases by curettage followed by the application of zinc chloride or cauterization. This treatment usually arrested the excessive haemorrhage and foul discharge for a time and was often repeated.

However, these two surgeons had been following the journals in which Wertheim's surgical methods were described and, as they were both first-class operators, began to perform radical abdominal hysterectomies on 2nd and even 3rd Stage cases. Unfortunately, most of those presenting themselves had reached the late 3rd and 4th Stages and occasional surgical attempts were made on these well established growths with the result that the immediate mortality was very high. Post-mortem examinations of the operative deaths showed that practically all were due to septic peritonitis.

When Lecturer in Gynaecology at the University of Sydney I reviewed the old records and the immediate death rate was well over 50 per cent.

As time and experience progressed they confined themselves to the earlier stages of the disease with a commendable reduction in mortality. In view of the fact that they had none of the advantages of blood transfusion, antibiotics or modern anaesthesia it was a wonder that more cases did not perish.

Thus the junior staff of the Gynaecology Department was educated in the purely surgical attack on carcinoma of the womb by Foreman and Thring in Australia and Victor Bonney in Britain. They never used radium or radiotherapeutic measures. Bonney was probably one of the few surgeons in Britain who persisted in the purely surgical attitude to the end.

About the year 1928 the late Dr. Frank Sandes, then Professor of Surgery, persuaded his old friend and fellow student, Sir Earle Page (an important member of the Commonwealth Cabinet) to purchase £100,000 of radium for Australia and Dr. Burrows was imported from Manchester to teach the local surgeons how to use it and for what cases it would be applicable.

Prior to Commonwealth action, Sir Hugh Dixson had provided the University with £5,000 worth of mesothorium and the Sydney University Cancer Fund had collected several

hundreds of thousands for deep X-ray machines and other forms of treatment.

Of course, about this time the late Dr. Chapman, the Professor of Physiology, the late Harold Molesworth, the late Patrick Moran, as well as the late Langloh Johnson and many others, turned against surgical aid for uterine cancer as did most other countries and preached that as much and even more could be accomplished by radium and deep radiation as by mutilating surgery.

Some of them even advocated and tried the method of lead injections as taught by Blair Bell of Liverpool.

To divert from the local scene, it is interesting to record that in Europe, mesothorium and radium were being given a full trial. Werner and his last assistant Sederl inform us that at Halle on Saale on Whitsun, 1913, Wertheim intended to deliver a comprehensive report on his operation for carcinoma of the neck of the womb dealing with cases that had been accepted in his Vienna Institute from October, 1909. His earlier successes were published in his standard work *Extensive Abdominal Operations for Carcinoma of the Neck of Womb.*

It was at that 1913 Congress, however, that, for the first time, extensive reports were presented on apparently successful cures following treatment with mesothorium and radium. All the speakers claimed excellent results but the cases had only been treated 6 to 18 months previously—not after the standard 5 years.

On that occasion his friend, Professor Döderlein, approached Wertheim, tapped his shoulder and said "My dear Wertheim, you are an historical personality. Your operation will not be performed any longer." Impressed by the reports on the supposedly successful treatment by mesothorium and radium and by Döderlein's words, Wertheim, who was to deliver his address in the afternoon, cancelled his announced lecture on that occasion.

Unfortunately, in that era none but Wertheim realized, from his experience 1898 to 1913, that the patient must be followed up for 5 years at least and if no signs or symptoms were discovered by physical examination at the end of that time the patient might be given a reasonable chance of permanent cure.

Today no recognized clinic would publish a cure rate under 5 years and at this hospital we have published our 10-year rate and now have 15- and 20-year cure rates which Dr. J. Solomon

TABLE I

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Cervicis Uteri, 1930–1958
Five-, Ten-, Fifteen- and Twenty-Year Survival and Cure Rates
(Compiled December, 1958)

Observation	Most Recent Five-Year Period 1949–1953	Five Years 1930–1953	Ten Years 1930–1948	Fifteen Years 1930–1943	Twenty Years 1930–1938
All patients examined with a view to treatment ..	374	1,126	752	487	296
All patients treated	360	1,071	711	465	286
Alive without recurrence	158	413	200	81	32
Alive with recurrence	5	13	2	—	—
Died of carcinoma	182	652	509	298	183
Died of intercurrent disease	4	19	26	39	33
Death due to unknown disease	—	—	—	35	23
Lost or not followed up	25	29	13	34	25
Cure rate amongst all patients examined (per cent) ..	42·2	36·7	26·6	16·6	10·8
Survival rate amongst all patients examined (per cent)	43·6	37·8	26·9	16·6	10·8
Cure rate amongst all patients treated (per cent) ..	43·9	38·9	28·1	17·9	11·2
Survival rate amongst all patients treated (per cent) ..	45·3	39·8	28·4	17·9	11·2

Up to December, 1958, 1,488 patients were examined with a view to treatment: 814 patients were treated surgically (operability rate 54·7 per cent); 26 patients died after operation (operative mortality rate 3·2 per cent).

has compiled from our King George V Memorial Hospital records. You must realize that our percentage of cures extends over nearly 30 years, and that the latest 5-years statistics are better than the overall 30-years average. (Table I.)

Of course, many other methods of attacking cancer of the womb were tried out. In 1951 I discussed with the Professor of Gynaecology at Barnes Hospital, St. Louis, the results of the gold injection and the radioactive gold wire which was inserted through the fornices into the parametrium surrounding the uterus. He admitted it was only in the experimental stage and naturally no results could be given until after the lapse of 5 years. Very little has come out of these experiments since.

When Dr. Burrows demonstrated for me the application of radium in the Anderson Stuart Theatres in 1928 I, as an off-shoot of the old surgical education, felt somewhat sceptical about the lasting results of radiotherapy, although I could not close my eyes to the local healing effect on malignant cervices. Even after seeing many almost miraculous local surface healings my mind was uneasy about embalmed cells in the underlying tissue and it was not long before we came across dying patients who had had full dosages of radiotherapy, with cancer deposits in the lymphatic glands and in the deep tissue of the cervix.

Consequently, in 1930 we adopted for good and all the combined treatment of 7,000 mg. hours of radium followed by radical Wertheim's hysterectomy 5 to 6 weeks later. The combined method had the advantage that all radium-treated uteri and the lymphatic glands could be submitted to pathologists and they soon discovered that many cases were insensitive to radiation and found live cancer cells in the deep cervical tissue of apparently healed cervices and always found that no effect whatever was made on metastates in the lymphatic glands.

As you will see from Table II the operation itself was attended by a high mortality in its early days, mostly owing to the then dreadful complication of peritonitis and to the fact that it was a difficult technical procedure attempted by too many unskilled surgeons. However, it was the first and only hope to be offered and, in expert hands, the operability rate has gradually increased and the primary mortality has been slowly but consistently reduced and the absolute 5-year cure rate, as shown in Tables II and III much improved.

TABLE II

Operation	Proportion of Patients Fit for Operation (Per cent)	Primary Mortality Rate (Per cent)
Wertheim (his first 500 cases)	49·0	19·0
Wertheim (his second 500 cases)	48·0	13·0
Second Vienna University Women's Clinic (Kermauner, Weibel, 1924–1936)	55·3	8·3
G. A. Wagner (Berlin Charité, 1928–1943)	41·1	14·8
Antoine (Vienna, Lainz, 1937–1940)	42·85	4·34
First Vienna University Women's Clinic (Schauta, Peham, 1901–1934)	54·7	6·6
Stoeckel (Berlin, University Women's Clinic, 1933–1937)	30·0	6·2
Amreich (Innsbruk, 1936–1939)	41·7	8·0
Amreich (Vienna, First University Women's Clinic, 1939–1943)	73·9	14·6
Werner (Vienna, Rudolf Foundation, 1939–1940)	78·58	7·96
Werner (Vienna, Lainz, 1940–1950)	76·35	6·0
Bonney (his first 500 cases)	63·0	14·0
Royal Prince Alfred Hospital, Sydney, 1930–1951 (635 cases)	51·4	3·9

All our cases had pre-operative radium of 7,000 mg. plus the advantage of blood transfusions and antibiotics, etc.

TABLE III

Comparative Results of Absolute Cure (Five Years)

Operation	Prevailing Type of Operation	Absolute Cure Rate (Per cent)
Wertheim (1898–1916)	Wertheim	18·6
Second University Women's Clinic, Vienna (Wertheim, Kermauner, 1916–1923)	Wertheim	26·9
Second University Women's Clinic, Vienna (Kermauner, Weibel, 1924–1936)	Wertheim	36·1
Antoine (Vienna, Lainz, 1937–1940)	Wertheim	36·6
First University Women's Clinic, Vienna (Schauta, Peham, 1901–1934)	Schauta	26·0
Stoeckel (Berlin, University Women's Clinic, 1933–1937)	Schauta	36·5
Stoeckel (Berlin, University Women's Clinic, 1938)	Schauta	42·1
Amreich (Innsbruk, 1936–1939)	Schauta—Amreich	36·1
Amreich (Vienna, First University Women's Clinic, 1939–1943)	Schauta—Amreich	34·1
Werner (Vienna, Rudolf Foundation, 1934–1940)	Wertheim	46·44
Werner (Vienna, Lainz, 1940–1945)	Wertheim	48·19
Bonney (London, first 500 cases)	Wertheim	40·0
Royal Prince Alfred Hospital (Sydney, 1930–1946)	Wertheim plus radium	55·3

TABLE IV

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Cervicis Uteri
Five-Year Survival Rates, 1930–1953
(Compiled December, 1958)

Treatment	Stage O		Stage I		Stage II		Stage III		Stage IV		Total	
	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive
Application of radium plus surgery	26	22 (84·6)	109	79 (72·5)	288	166 (57·6)	166	78 (46·9)	—	—	589	345 (58·6)
Application of radium alone	—	—	12	7 (58·3)	86	23 (26·7)	253	40 (15·8)	105	6 (5·7)	456	76 (16·7)
Application of radium plus incomplete surgery	—	—	2	1 (50·0)	6	1 (16·7)	15	3 (20·0)	3	— (0)	26	5 (19·2)
No treatment	—	—	—	—	—	—	6	— (0)	49	— (0)	55	— (0)
Total	26	22 (84·6)	123	87 (70·7)	380	190 (50·0)	440	121 (27·5)	157	6 (3·8)	1,126	426 (37·8)

(Percentages in brackets)

TABLE V

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Cervicis Uteri
Ten-Year Survival Rates, 1930–1948
(Compiled December, 1958)

Treatment	Stage O		Stage I		Stage II		Stage III		Stage IV		Total	
	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive
Application of radium plus surgery	11	9 (81·8)	48	29 (60·4)	175	78 (44·6)	120	51 (42·5)	—	—	354	167 (47·2)
Application of radium alone	—	—	6	1 (16·7)	56	10 (17·9)	190	18 (9·5)	89	4 (4·5)	341	33 (9·7)
Application of radium plus incomplete surgery	—	—	1	1 (100)	3	1 (33·3)	9	— (0)	3	— (0)	16	2 (12·5)
No treatment	—	—	—	—	—	—	2	— (0)	39	— (0)	41	— (0)
Total	11	9 (81·8)	55	31 (56·4)	234	89 (38·0)	321	69 (21·5)	131	4 (3·1)	572	202 (26·9)

(Percentages in brackets)

TABLE VI

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Cervicis Uteri
Fifteen-Year Survival Rates, 1930–1943

(Compiled December, 1958)

Treatment	Stage O		Stage I		Stage II		Stage III		Stage IV		Total	
	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive
Application of radium plus surgery	—	—	30	13 (43·3)	104	31 (29·8)	90	25 (27·8)	—	—	224	69 (30·8)
Application of radium alone	—	—	3	— (0)	33	4 (12·1)	122	4 (3·3)	71	4 (5·6)	229	12 (5·2)
Application of radium plus incomplete surgery	—	—	—	—	—	—	10	— (0)	2	— (0)	12	— (0)
No treatment	—	—	—	—	—	—	1	— (0)	21	— (0)	22	— (0)
Total	—	—	33	13 (39·4)	137	35 (25·5)	223	29 (13·0)	94	4 (4·3)	487	81 (16·6)

(Percentages in brackets)

TABLE VII

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Cervicis Uteri
Twenty-Year Survival Rates, 1930–1938

(Compiled December, 1958)

Treatment	Stage O		Stage I		Stage II		Stage III		Stage IV		Total	
	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive
Application of radium plus surgery	—	—	19	4 (21·1)	62	17 (27·4)	48	7 (14·5)	—	—	129	28 (21·7)
Application of radium alone	—	—	2	— (0)	13	— (0)	86	1 (1·2)	49	3 (6·1)	150	4 (2·6)
Application of radium plus incomplete surgery	—	—	—	—	—	—	5	— (0)	2	— (0)	7	— (0)
No treatment	—	—	—	—	—	—	1	— (0)	9	— (0)	10	— (0)
Total	—	—	21	4 (19·0)	75	17 (22·7)	140	8 (5·7)	60	3 (5·0)	296	32 (10·8)

(Percentages in brackets)

TABLE VIII

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Cervicis Uteri
Survival Rates During Most Recent Five-Year Period, 1949–1953

(Compiled December, 1958)

Treatment	Stage O		Stage I		Stage II		Stage III		Stage IV		Total	
	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive	Number	Alive
Application of radium plus surgery	15	12 (80·0)	61	44 (72·1)	113	68 (60·2)	46	20 (43·5)	—	—	235	144 (61·3)
Application of radium alone	—	—	6	3 (50·0)	30	6 (20·0)	63	9 (14·3)	16	— (0)	115	18 (15·7)
Application of radium plus incomplete surgery	—	—	1	— (0)	3	— (0)	6	1 (16·7)	—	— (0)	10	1 (10)
No treatment	—	—	—	—	—	—	4	— (0)	10	— (0)	14	— (0)
Total	15	12 (80·0)	68	47 (69·1)	146	74 (50·7)	119	30 (25·2)	26	— (0)	374	163 (43 6)

(Percentages in brackets)

TABLE IX

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Cervicis Uteri
Five-, Ten-, Fifteen- and Twenty-Year Survival Rates, 1930–1953
(Compiled December, 1958)

Treatment	Most Recent Five-Year Period 1949–1953 (Per cent)	Five-Year Survival Rate 1930–1953 (Per cent)	Ten-Year Survival Rate 1930–1948 (Per cent)	Fifteen-Year Survival Rate 1930–1948 (Per cent)	Twenty-Year Survival Rate 1930–1938 (Per cent)
Application of radium and/or surgery	61·3	58·6	47·2	30·8	21·7
Application of radium alone	15·7	16·7	9·7	5·2	2·6
Application of radium plus incomplete surgery	10·0	19·2	12·5	0	0
No treatment	0	0	0	0	0
Total	43·6	37·8	26·9	16·6	10·8

TABLE X

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Cervicis Uteri
Five-, Ten-, Fifteen- and Twenty-Year Survival Rates, 1930–1953—Adenocarcinoma Compared with Squamous Carcinoma
(Compiled December, 1958)

Type of Carcinoma	Five-Year Survival Rate 1930–1953	Ten-Year Survival Rate 1930–1948	Fifteen-Year Survival Rate 1930–1943	Twenty-Year Survival Rate 1930–1938
Squamous Carcinoma:				
Number examined	1,053	696	452	270
Alive	410	193	77	30
	38·9%	27·7%	17·4%	11·1%
Adenocarcinoma:				
Number examined	73	56	35	26
Alive	16	9	4	2
	21·9%	16·1%	11·4%	7·7%

TABLE XI

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Cervicis Uteri
Five-, Ten-, Fifteen- and Twenty-Year Survival Rates, 1930–1953—Patients with Gland Involvement
(Compiled December, 1958)

	Five-Year Survival Rate 1930–1953	Ten-Year Survival Rate 1930–1948	Fifteen-Year Survival Rate 1930–1943	Twenty-Year Survival Rate 1930–1938
Patients submitted to radical surgery	589	354	235	136
(*a*) Patients found not to have glands involved	463	281	184	111
	78·6%	79·4%	78·3%	81·6%
(*b*) Patients found to have glands involved ..	126	73	51	25
	21·4%	20·6%	21·7%	18·4%
Alive in Group (*a*)	311	154	64	28
	67·2%	54·8%	34·8%	25·2%
Alive in Group (*b*)	37	13	4	1
	29·4%	17·8%	7·8%	4·0%

The late Professor Werner proffered the opinion that the improvements that have been achieved over the years in the way of an absolute permanent 5-year cure are not so much due to an extension of the radical character of the operation as they are to earlier diagnosis and to the reduction of primary mortality through the use of blood transfusion, antibiotics, good anaesthesia and efficient nursing plus the help of radioactive substances.

Let us keep our feet on the ground and accept nothing but the 5, 10, 15 and 20 years results after the known curative methods have been applied.

We all hope that the scientific investigations upon which millions of pounds have been or are being spent will one day produce a cure for cancer such as Salvarsan and other drugs did for syphilis. Until such a remedy is discovered we must use the present-day methods at our disposal.

We at King George V Hospital are convinced that the best method is to clean up the ulceration of the cervix with radium so that any operative procedure undertaken will be carried out in a clean field. Foreman's and Thring's surgical experience in operating while an infected area existed showed that practically all their deaths were due, not to bad surgery, but to septic peritonitis.

Today at King George V we realize that surgery must only be undertaken when the vaginal and cervical areas have been cleaned by radium. We know from experience that only 15 to 20 per cent of operated cases display lymph involvement so the very extensive operations beyond Wertheim's original technique such as pelvic evisceration will not affect the 5- to 20-year cure rate to a very great extent.

It is now well established that the earlier the treatment the better the result. Thus the whole of the energy of King George V Hospital staff is now being concentrated on colposcopy and the Papanicolaou test. These methods for early diagnosis select cases for cervical biopsy and so allow the diagnosis of cancer to be made in women with minimal or even no symptoms and who have an apparently innocent cervix on ordinary methods of examination. Most of these cancers are in the early or pre-invasive stage, in which surgeons can attain a nearly 100 per cent cure rate. To detect carcinoma in this early stage in as many cases as possible must be our aim.

As the growth advances, the results become progressively worse and worse: 1st stage 75 to 80 per cent; 2nd stage 45 to 50 per cent; 3rd stage 25 per cent might be the average of 5-year cures in the other Australian States and overseas countries. Those who claim any 5-year

TABLE XII

Royal Prince Alfred Hospital, Sydney, N.S.W.—Carcinoma Corporis Uteri
Five- and Ten-Year Cure and Survival Rates, 1930–1953
(Compiled December, 1958)

Observation	Five Years	Ten Years
All patients examined with a view to treatment	298	158
All patients treated	288	153
Alive without recurrence	170	69
Alive with recurrence	9	0
Died of carcinoma	90	60
Died of intercurrent disease	17	20
Lost or not followed up	12	9
Cure rate amongst all patients seen (per cent)	57·0	43·7
Survival rate amongst all patients seen (per cent)	60·0	43·7
Cure rate amongst all patients treated (per cent)	59·0	45·1
Survival rate amongst all patients treated (per cent)	62·2	45·1

Up to December, 1958, 465 patients had been examined with a view to treatment: 365 patients were treated surgically (operability rate, 78·5 per cent), 9 patients died after operation (operative mortality, 2·5 per cent).

TABLE XIII

Royal Prince Alfred Hospital, Sydney, N.S.W.—Five- and Ten-Year Survival Rates of Carcinoma Corporis Uteri, 1930–1953
(Compiled December, 1958)

	Five-Year Survival						Ten-Year Survival					
	Number	Alive	Post-operative Deaths	Other Deaths	Lost	Survival Rate (Per cent)	Number	Alive	Post-operative Deaths	Other Deaths	Lost	Survival Rate (Per cent)
Application of radium and surgery or surgery alone ..	232	168	6	48	10	72·4	117	66	2	42	7	56·4
Application of radium alone or radium plus deep X-rays	39	4	3	30	2	10·3	26	1	3	21	1	3·8
Application of radium plus incomplete surgery or incomplete surgery alone ..	17	7	4	6	0	41·2	10	2	3	4	1	20·0
No treatment	10	0	0	10	0	0	5	0	0	5	0	0
Total	298	179	13	94	12	60·0	158	69	8	72	9	43·7

TABLE XIV

Royal Prince Alfred Hospital, Sydney, N.S.W.
Carcinoma Corporis Uteri, 1949–1953
Survival Rate During Most Recent Five-Year Period
(Compiled December, 1958)

Observation	Five Years
All patients examined with a view to treatment ..	139
All patients treated	134
Alive without recurrence	83
Alive with recurrence	4
Died of carcinoma	40
Died of intercurrent disease under 5 years ..	4
Lost or not followed up	8
Cure rate amongst all patients seen (per cent) ..	59·7
Survival rate amongst all patients seen (per cent)	62·6
Cure rate amongst all patients treated (per cent) ..	61·9
Survival rate amongst all patients treated (per cent)	64·9

cure results in the 4th stage of carcinoma of the cervix might have grouped their cases wrongly or not taken a biopsy. However we must admit that a very few non-vicious growths might be held in check by radiological measures alone.

I think there is little argument today about the advisability of surgery for cancer of the corpus uteri and, in many cases, added lymphadenectomy. Most agree with the complete excision of vulval cancers with extensive excision of the draining lymphatic glands. The occasions when the gland of Cloquet and the internal iliac glands are to be removed must be left to the expert in this region.

The Profession, I hope, will come to realize that all female pelvic cancers should be referred to well-established cancer centres where experienced surgeons in all specialties, pathologists,

TABLE XV

Royal Prince Alfred Hospital, Sydney, N.S.W.
Five-Year Survivals in 298 Cases of Carcinoma Corpus Uteri, 1930–1958
(International Classification)

Type of Carcinoma	Number of Cases	Alive with No Recurrence at Five Years (Per cent)
Carcinoma corpus uteri:		
Stage O	4	3 (75)
Stage I:		
Group 1	227	158 (69·6)
Group 2	18	1 (5·6)
Stage II	32	4 (12·5)
Total	277	163* (58·8)
Carcinoma corporis et endocervicis	11	1 (9·1)
Carcinoma uteri et ovarii	6	3 (50·0)

* Nine other patients were alive with recurrence at end of five years.

radiotherapeutists and statisticians form a team. It is pathetic to see the general practitioner attempting this work. I have in my time come across many cases where a subtotal hysterectomy had been done by an occasional surgeon for uterine bleeding and found the cervix, the original site of attack, still bleeding and the disease extending on to the vaginal walls.

The follow-up of our present cancer statistics shows a gradual increase in the number of untraced cases. The population of Australia now exceeds ten millions and among the increase is a large number of immigrants who are unable to write or speak English or who frequently change residence from State to State.

In the 15- and 20-years follow-up, the number of deaths from unknown causes should not be assessed as due only to cancer as many may have died from the ravages of old age. Again in these tables many who registered regularly for 10 years drop out, as they consider themselves cured.

While writing this paper a patient reported at the age of 72 with no signs of recurrence. She had radium and Wertheim's for Stage II squamous carcinoma in 1933 and had not reported after 1949.

The statistics record the work of the whole staff of the King George V Memorial Hospital within the Royal Prince Alfred Hospital from 1930 to 31st December, 1958. Drs. F. P. Pigott and H. J. Solomon compiled the Cervix Uteri Tables and Dr. Malcolm Coppleson the Corpus Uteri Tables.

The King George V Memorial Hospital statistics for Cancer of the Vulva have already been published by Dr. Malcolm Stening and Dr. P. M. Elliott.

THE CLINICAL APPLICATION OF ENDOMETRIAL PHOSPHATASE DETERMINATIONS

BY

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IN recent years the enzymatic activity of the endometrium during the menstrual cycle has several times attracted the attention of investigators. This is understandable, for there are only few tissues in the human organism which show, in such a short time, such profound morphological changes accompanied by biochemical changes catalyzed by enzymes. The maximum activity of most enzymes has been shown to occur in the late proliferative stage and the early secretory phase. Of the various enzymes it is especially the phosphatases which have been the subject of study, mainly histochemical in nature.

The present paper is concerned with an effort to determine the progestational activity of the organism by quantitative determinations of alkaline and acid phosphatase of the human endometrium. A pre-menstrual rise of the acid and a fall of the alkaline phosphatase was accepted as a criterion of good progestational activity.

To determine the progestational activity of the organism, we always use the morphological picture, the degree of the glandular development of the uterine mucosa. Although this morphological examination remains indispensable for us, we know that it does not come up to all requirements. There is a need for a quantitative biochemical method to supplement the morphological picture in special cases.

DEFINITION OF PHOSPHATASES

A phosphatase is an enzyme which catalyzes the hydrolytic splitting of organic phosphoric acid compounds. It is possible to distinguish a number of forms based on the substrates on which these enzymes act and for which they possess a certain degree of specificity. Phosphomono-esterase is the most important of these enzymes; in general it is briefly called "phosphatase".

In the endometrium an acid phosphatase with an optimum pH between 4 and 5, and an alkaline phosphatase with an optimum pH round about 9, have been demonstrated.

For a general survey of the physiological significance of the phosphomono-esterases we refer to the publication of Moog (1945).

THE POSSIBLE FUNCTIONS OF THE PHOSPHATASES IN THE ENDOMETRIUM

There are numerous theories on the functions of the phosphatases. It should however be realized that this esterase forms only a part of the intricate ferment system, various components of which catalyze a great number of important chemical processes in the cells, fluids and in secretions.

In the endometrium a relationship has been shown to exist between proliferation and alkaline phosphatase activity (Hedberg, 1950; Hughes, 1950; Velardo, 1954).

The decrease of the alkaline phosphatase in the secretory phase cannot alone be attributed to the influence of the oestrogens, because the second peak of oestrogen production falls precisely in the second half of the secretory phase (as judged by the urinary excretion of

oestrogens). It is probably due to an inhibiting effect of progesterone (Velardo, 1954).

The activity of the alkaline phosphatase falls with the progesterone activity; at the same time a rise of the activity of the acid endometrial phosphatase is observed (Goldberg and Jones, 1953, 1954; MacKay, Hertig, Bardawil and Velardo, 1956). The properties of the acid phosphatase of prostate and endometrium are to a great extent similar. Their similar behaviour with respect to various substrates and inhibitors led Goldberg and Jones to conclude that the acid phosphatases of the organs concerned may have corresponding functions.

According to many investigators it is not improbable that the alkaline phosphatase of the endometrium, which is stimulated by the oestrogens, forms a link in the intricate mechanism of carbohydrate (Atkinson and Engle, 1946; Arzac and Blanchet, 1948), protein (Moog, 1945) and phospholipid metabolism (Antoine, 1954) of the uterine mucosa, but that it is also of importance for fertilization, together with the acid phosphatase (Burton, 1953). Until recently the alkaline phosphatase has been regarded as a ferment with an exclusively hydrolytic function, but it has now been proved to act as a phosphokinase as well, i.e., that it is able to catalyze the transmission of phosphoric acid from one organic molecule to another.

We are not able to give an exact explanation of the functions of the phosphatases and it is not clear why there are two forms: alkaline and acid phosphatase. It is beyond doubt that these two are indeed different enzymes (Moog, 1945; Woodard, 1951; Gomori, 1952). The alkaline form is the more widespread of the two, and its concentration is normally higher than that of the acid phosphatase. This difference may mean that the function of the alkaline phosphatase is more directed to the tissues as a whole, and that the acid form is of more specific importance for the metabolism of certain kinds of cells.

We believe that this theory might also be applied to the endometrium. According to Moog, the simultaneous presence of these two phosphatases would enable the cells to display different cellular activities at the same time, thus favouring the economy of the cell-function.

Methods of Studying the Phosphatases

The phosphatases may be studied by *histochemical* and *biochemical* methods. In both methods inorganic phosphate is liberated by the action of the phosphatase on the specific substrate; this inorganic phosphate is visualized in the preparation in an indirect way by means of a histochemical technique (Gomori), or may be determined colorimetrically by a biochemical method (Bodansky).

The presence, the localization and the cyclic changes of the phosphatases in the normal endometrium have been studied by many authors by means of the *histochemical* method of Gomori (1952) and adequately described (Atkinson and Engle, 1946, 1947; Arzac and Blanchet, 1948; Hall, 1950; Hughes, 1950; Ober, 1950; Burton, 1953; Willighagen, 1956).

In our investigation we used the method of Gomori modified according to Willighagen (for details see Jaszmann, 1958a). The results were consistent with the findings of the above-mentioned investigators.

The *biochemical* determination of phosphatase in the human endometrium is also of recent date. Jones, Wade and Goldberg (1952), Goldberg and Jones (1953, 1954, 1956) and Woodard (1956) especially deserve credit for their work in this field. Their methods differ as regards substrate, the concentration of the substrate, the optimum pH, etc. It seemed therefore useful to find out the most suitable conditions for the quantitative determination of the endometrial phosphatases. We had to carry out several preliminary experiments, on the choice of the substrate, the concentration of the substrate, the incubation period and the temperature at which the enzyme acted on the substrate. Further we studied the influence of the room temperature on the reaction speed, the dependence of the endometrial phosphatase on the pH and the influence of some inhibitors on the phosphatase activity.

Storage of endometrial tissue at a low temperature, and rapid homogenization with glass wool in a refrigerated mortar with cooled water, yielded a suitable extraction method both for the acid and the alkaline phosphatase. When a buffer prepared according to Michaelis was used, sodium-beta-glycerophosphate in a con-

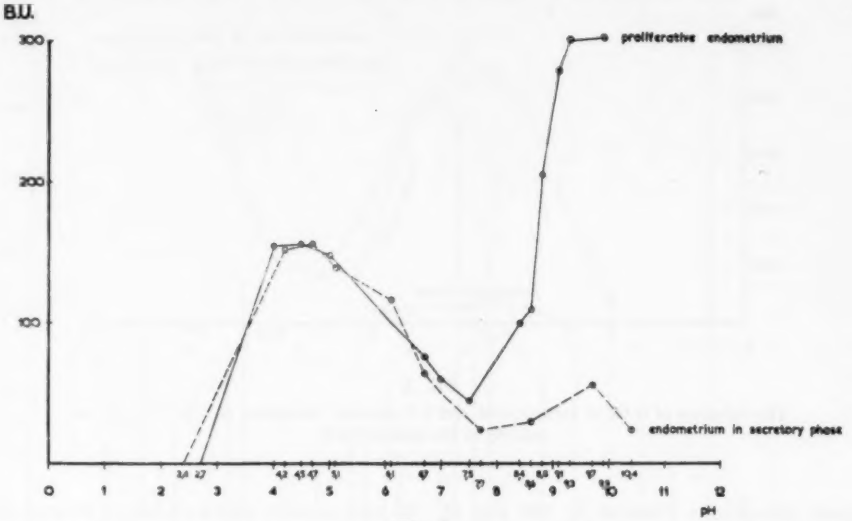

FIG. 1

The "organ curve" of the endometrium.

centration of 40 mg./ml. proved to be preferable to the alpha-modification. The incubation time was fixed at one hour at 37° C. It further appeared that in routine procedures the determination of the activity at pH 5 and pH 9 was sufficient after the previous preparation of a pH curve of the endometrial phosphatase both in the proliferative and in the secretory phase ("organ curve" of the endometrium).

To determine the optimum pH of the phosphatases in the proliferative phase we chose an endometrium which microscopically showed a light degree of cystic glandular hyperplasia, i.e., in which progesterone activity was almost certainly excluded.

For the determination of the activity curve in the secretory phase we chose an endometrium which microscopically showed evident signs of progestational activity (end of the secretory phase).

Figure 1 shows the two pH activity curves, expressed in Bodansky units and converted to the same quantity of starting material, so that comparison is possible.

To eliminate the influence of the acid erythrocyte phosphatase of the admixed blood when determining the pure endometrial phosphatase, the experiments at pH 5 were always carried out with the addition of 0·02 M tartaric acid (a powerful specific inhibitor of the acid endometrial phosphatase). It was thus possible to obtain a fairly accurate determination of acid endometrial phosphatase. Formaline 0·5 per cent was also used as an inhibitor in these experiments (Fig. 2).

With 0·02 M tartaric acid at pH 5 we found an inhibition of 93 per cent and 91 per cent, respectively, of the activity of the acid endometrial phosphatase, if the substrate was sodium-beta-glycerophosphate; an inhibition of 83 per cent was found with the alpha-modification as substrate.

The alkaline phosphatase determination did not cause particular difficulties. We used the technique of Bodansky, in which the values of the phosphatase activity were expressed in Bodansky units. A Bodansky unit (B.U.) corresponds to the number of milligrammes of

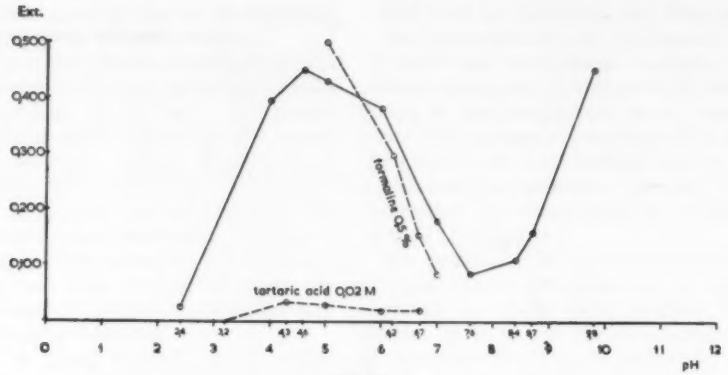

FIG. 2

The influence of 0·02 M tartaric acid and 0·5 per cent formaline on the phosphatase activity in the endometrium.

inorganic phosphorus liberated by 100 mg. of tissue, in our case fresh endometrial tissue (for details see Jaszmann, 1958a).

The biochemical method is indicated for quantitative enzyme determinations, while the histochemical method is preferable for qualitative and localization purposes. Most of the investigators in this field have used the histochemical method; they believed that their results justified quantitative conclusions. They called this method a "semi-quantitative" determination, which is however incorrect. In the living cells the phosphatase occurs in two forms: lyoenzyme (soluble form) and desmoenzyme (insoluble form) fixed on the components of the protoplasm. The lyoenzymes get almost certainly lost during the histochemical examination; it is probably only the desmoenzymes which are demonstrated. As the proportion between lyoenzymes and desmoenzymes differs from organ to organ, one should always employ both the histochemical and the biochemical techniques. The biochemical method has the advantage that it covers a larger part of the uterine mucosa; the histochemical technique, on the contrary, gives a picture of only a very small part of the endometrium.

When investigating the localization and the activity of phosphatases in the human endometrium, both methods should therefore always be used parallel with each other. In spite of the shortcomings of the two methods it is possible to make valuable observations on the phosphatase activity of the endometrium.

THE BIOCHEMICAL PHOSPHATASE DETERMINATION IN THE CLINIC

To obtain a correct picture of the changes in activity of the alkaline and acid phosphatase of the endometrium during the menstrual cycle, we first carried out a series of determinations on normal endometria. As a basis for the further study we tried to find a correlation between the parallel histochemical and biochemical determinations on the one hand and the usual haematoxylin-eosin method on the other.

We used 21 endometria (hysterectomy and curettage) for our standard investigation. This number was however too small to warrant reliable conclusions. Moreover, most of the patients were older than 35 years and many of them had been operated upon because of anatomical abnormalities. Thus we have to leave as an open question the degree to which organic changes exert an influence on the activity of the phosphatases. On the other hand, it is evident that, for example, an intramural myoma may cause local atrophy of the endometrium, resulting in a deficiency in phosphatase

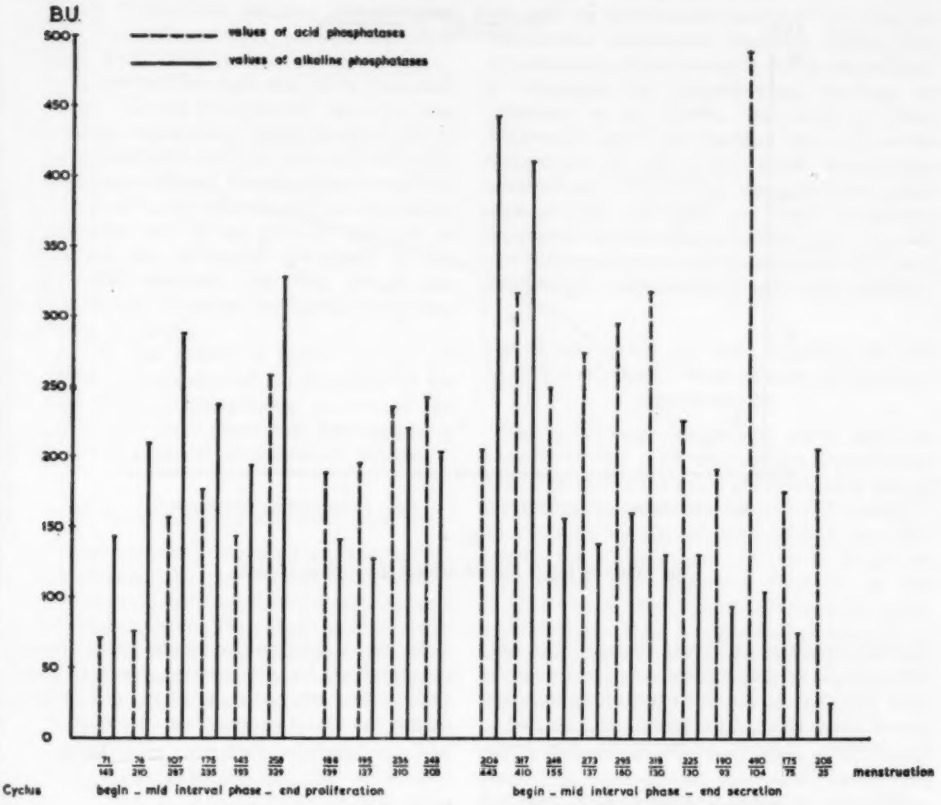

FIG. 3

Survey of the standard investigation of acid and alkaline phosphatase activity.

activity. Figure 3 gives a survey of the standard investigation; the phosphatase activity is expressed in B.U.

Discussion

We occasionally observed that as regards the activity of acid and alkaline phosphatase, the values of Bodansky units obtained often differed from each other, although the same picture was found in the phase determination.

More detailed investigation showed that the density of glands or stroma found on histological examination was a factor which had certainly to be taken into account.

According to the histochemical method, the phosphatase activity is largely limited to the epithelium of the glands; it is natural that the values were higher in an endometrium which was rich in glands than in oedematous stroma with a low number of glands per visual field.

This is certainly also an argument in favour of parallel histochemical and biochemical determinations in all cases.

When determining the functional activity of

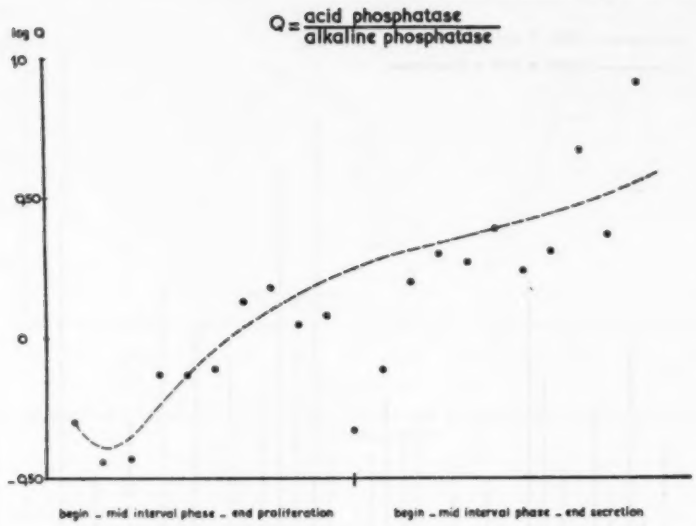

FIG. 4

The values of log Q plotted against the various phases.

the endometrium, we should therefore not only keep account of the absolute values in Bodansky units obtained by the biochemical method, but also of the density of the glands with respect to the stroma, judged according to the histochemical method.

Although our small number of cases does not warrant statistical conclusions, we still believe that a rise of the acid and a fall of the alkaline phosphatase activity is a criterion of good progestational activity. It is perhaps possible to express the ratio of the acid and alkaline phosphatase activities as a fraction, in which the value of the acid phosphatase is placed in the numerator and that of the alkaline in the denominator. In a proliferative phase we find for example 71/143=0·496; in an early secretory phase 190/93=2·04; in a menstruating endometrium 205/25=8, etc. This may perhaps yield an index more easy to use in practice (e.g., in cases of sterility or pathological conditions) than one based on the absolute values in Bodansky units based on the density of glands in the stroma per visual field.

To give a survey of the results of the standard investigation, we plotted the values of log Q against the various phases of the endometrium during the investigation (Figs. 3 and 4).

$$Q = \frac{\text{activity of alkaline phosphatase}}{\text{activity of acid phosphatase}},$$

both of them expressed in B.U.

Q	log Q	Q	log Q
0·497	0·70–1	0·465	0·67–1
0·362	0·56–1	0·77	0·89–1
0·372	0·57–1	1·60	0·20
0·745	0·87–1	1·99	0·30
0·740	0·87–1	1·84	0·27
0·784	0·89–1	2·44	0·39
1·35	0·13	1·73	0·24
1·53	0·18	2·04	0·31
1·12	0·05	4·72	0·67
1·20	0·08	2·34	0·37
		8·18	0·91

Most of the points are distributed near the curve represented by a dotted line in the figure.

The two points which lie far from the curve (Nos. 11 and 12) may be explained as follows:

No. 11, a 53-year old patient, had irregular periods; the endometrium showed an early secretory phase with a non-corresponding Q, which, in view of her age, was to be expected. Patient No. 12 was 44 years old; here also the histologically determined early secretory phase did not correspond with the expected value for Q; should the standard investigation be reliable, we should not only take account of the phase and the value of Q, but also of age and its bearing on the hormonal condition of the patients (for example, the first group was between 20 and 35 years, the second group was older than 35 years).

When, in the future, a larger amount of material has been collected for the study of the acid and alkaline phosphatase activity of the endometrium, it may prove that this method is suitable as an index of progestational activity.

The Pathological Endometrium

So far the correlation between the morphology and the function of the normal endometrium cannot serve as a criterion for the pathologically changed endometrium. Here there exists perhaps an even greater need for a biological test based upon morphological methods. It is a well-known fact that it is often difficult to give a functional interpretation of the morphological findings in the histopathology of the endometrium. The cells and the tissues possess only a limited capacity of reacting with morphological changes to functional disturbances.

We have had the opportunity of studying various pathological endometria including four cases of hyperplasia glandularis cystica. We conceived the idea that the quantitative alkaline (if need be with the acid) phosphatase determination of the endometrium might give a better impression of the oestrogenic activity of the organism, than methods based on the analysis of urine, faeces and serum (Wahlen, 1950).

We also studied an endometrium of a patient with genital tuberculosis. The phosphatase activity was lower than we had so far observed. We cannot decide from this single case the degree to which age (48 years) or the specific inflammation can be held responsible.

It was an unfortunate fact that there was no endometrial carcinoma available during this investigation, so that we were not in the position to complete the histochemical findings of Atkinson *et al.* (1949). As early as 1952, Atkinson, Gall and Gusberg pointed to the importance of the biochemical quantitative examination: "However, since alkaline phosphatase and glycogen are both irregularly distributed in endometrial carcinoma, a correlation between the two substances cannot be drawn conclusively until quantitative data are available."

The Stimulation of the Activity of the Acid Endometrial Phosphatase by Methyloestrenolone

The preceding experiments show that the activity of the acid endometrial phosphatase and of progesterone run a parallel course during the cycle. Although the influence of oestrogen on the alkaline phosphatase activity has been known for a long time, in the literature no experiments are described directed to the stimulation of the activity of the acid endometrial phosphatase by means of progestational substances. As far back as 1946 Atkinson and Elftman made an effort to study the changes in alkaline phosphatase activity in castrated mice after administration of oestrogens, progesterone and androgens; they used the histochemical method of Gomori. No acid phosphatase was observed. After the administration of oestrogenic substances an increased alkaline phosphatase activity was observed: progesterone and testosterone did not cause this effect. Oestrogens administered in combination with progesterone yielded a picture as if only oestrogens had been given.

Recently new synthetic steroids have become available—17-alkyl-19-nortestosterone compounds—which possess a powerful progestational activity. Of these compounds, methyloestrenolone (Orgasteron) administered by mouth proved to have ten times the activity of the same amount of progestine administered intramuscularly. Of late Orgasteron has often been used with success for clinical purposes, for example in menopausal haemorrhages (Jaszmann, 1958b).

In four cases we administered methyloestrenolone in a dosage of 5 mg. daily for five days (in 3 cases directly after menstruation and in 1 case during menstruation). Subsequently hysterectomy was carried out because of anatomical changes, during which the ovaries were inspected or removed with the uterus. In the first three cases we found that, after the administration of this strongly progestational substance, the endometrium, even in the proliferative phase and in the absence of ovulation can show a progestational picture with a correspondingly higher acid and lower alkaline phosphatase activity. The basal temperature also rose after administration of this synthetic substance. The methyloestrenolone, administered during menstruation, also caused an uncommonly high acid phosphatase activity on the 7th day of the cycle before the regeneration stage. Two cases are described below.

No. 4791, age 34, cycle 28/4 days. The last menstruation had taken place on 16th–20th June. The patient had been given Orgasteron 5 mg. daily from 20th–24th June, inclusive, i.e., directly after menstruation. She was operated upon on the 9th day of the cycle for carcinoma of the portio (Wertheim).

Histological examination: the endometrium contained markedly tortuous glands, all of which showed a regular row of big subnuclear vacuoles. The picture was that of an active early secretory phase about three days after ovulation. The ovaries contained follicle cysts and a corpus luteum in regression, but no ruptured mature follicle. We had therefore to assume that the basal secretion vacuoles had been caused by the methyloestrenolone administered.

Histochemical examination: there was a considerable alkaline phosphatase activity in an apical border in the epithelium of all glands. The acid phosphatase reaction was also considerable, especially subapically in the epithelia, below the border of the alkaline phosphatase but to a lesser degree also basally.

Biochemical examination: the acid phosphatase activity was 792 B.U. and the alkaline 752 B.U.

No. 6072, age 43, cycle 26/28: 6–7 days, last menstruation on 12th August. During menstruation (14th–19th August) the patient was given Orgasteron 5 mg. daily. On 20th August a supravaginal hysterectomy was carried out because of myoma; the adnexa were spared.

Histological examination revealed an early proliferation phase; the glands were in general narrow. There was no secretion, and there were few mitoses. Occasionally islets of pseudo-decidually changed mucosa were observed, but without secretion. Probably the desquamation had not been complete as a result of the methyloestrenolone administered.

Histochemical examination showed a moderately alkaline phosphatase reaction in an apical border of the epithelium of the glands. The blood vessels also showed some activity. There was a slight acid phosphatase reaction, limited to the apical part of a proportion of the glandular epithelia.

Biochemical examination: the acid phosphatase activity was 280 B.U. and the alkaline 163 B.U.

Discussion

A recent publication of Lutwak-Mann and Adams (1957) describes an effort to use enzyme activity as an index of the effect of various progestational substances. The activity of carbonic anhydrase, which is related to the progestational activity of the organism, proved to vary—in the endometrium of rabbits—proportionately with the strength of the progestational substances administered. All test animals had to be well-bled to eliminate the activity of the carbonic anhydrase of the erythrocytes. So far no experiments have been carried out in this respect on the human endometrium.

Our acid phosphatase determination, although technically somewhat more laborious than for example the determination of the carbonic anhydrase, enables us to determine the pure acid endometrial phosphatase with the help of specific inhibitors, also in the presence of erythrocytes. The material for the examination can be obtained by curettage, even by microcurettage.

We are aware of the fact that these few cases cannot form the basis for conclusions. On the other hand, we have obtained a strong suggestion that after administration of hormones changes in the activity of the endometrial phosphatase are to be expected. A wide field for further research is therefore still open.

Summary

The author's purpose has been to make a contribution to our knowledge of the biochemistry of the human endometrium during the menstrual cycle, in particular of the phosphatases.

A method was elaborated for the quantitative determination of the phosphatases in the human

endometrium, which may be suitable for clinical application.

During the proliferative stage the alkaline phosphatase dominates, in the secretory phase the acid phosphatase. The author regards a high acid and a low alkaline phosphatase activity in the late secretory phase as an index of a good progestational activity. When a greater amount of material has been collected for the determination of the acid and alkaline phosphatase activity of the endometrium, it may prove that the method described should be included in the examination schema for sterility as an index of the progestational activity of the genital tract.

Acknowledgments

I wish to thank Professor Dr. A. J. M. Holmer, University of Leyden, for stimulating this work, Dr. C. L. Harders, head of the Biochemical Laboratory, Gemeente Apotheek, The Hague, for his help and advice on the solution of biochemical problems in connexion with this investigation, and Dr. P. Bakker, Pathologist, for his help with the interpretation of the histochemical data. I should like to thank Dr. K. A. F. Houwert, Gynaecologist, Gemeente Ziekenhuis Zuidwal, The Hague, in whose department this work was done, for his encouragement. Thanks are due to Miss C. W. F. van Renesse van Duivenbode and Miss J. M. L. C. Lasance for their skilled technical assistance.

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VARIATIONS IN THE MALIGNANCY OF CANCERS OF THE UTERINE CERVIX

BY

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CANCERS of the uterine cervix vary so much in their aggressive qualities that survival figures which express statistical averages are not applicable to the individual. Some cancers run a relatively benign course, whereas others spread rapidly and are soon fatal, so that therapy has its unexpected successes and unaccountable failures.

Any series of cases is a complex of tumours of widely different behaviour patterns—tumours which differ in rate of growth, invasiveness and disseminating properties—and this variation in behaviour is emphasized when the cases are grouped on the basis of symptom-duration. In Table I all cases of cancer of the uterine cervix seen at the Cardiff Royal Infirmary during the years 1940–1954 are classified into four groups according to the reported length of history, which in this survey represents the time elapsing from the patient noticing the first symptom to the day she is seen at hospital with a view to treatment.

It is evident that the four groups are not comparable. If the growths had all been similar in character, the longer the history, the greater would be the percentage of advanced growths, and also the number of deaths within the five-year period. But the extent of the disease when first seen was not primarily determined by the length of history, and there is no significant difference in the proportion of early cases in the four groups. Consequently one would have expected the survival rates in the four groups to be similar, but in fact they are only similar in the first three groups. With histories up to 12 months, survival was largely independent of symptom-duration, but significantly better results were obtained in those women who delayed for more than a year (Group D), and this difference would have been still more

TABLE I

Distribution of Cases by Symptom-Duration

(Percentages in brackets)

Group	Symptom Duration in Months	Number of Cases Seen	Number Seen in Stages 1 or 2	5-Year Survivors
	0– 1	45	32 (71)	20 (44)
	– 2	54	35	24
	– 3	88	49	20
		—	—	—
A	0– 3	187	116 (62)	64 (34)
B	– 6	250	139 (56)	73 (29)
C	–12	262	151 (58)	79 (30)
D	Over 12	225	142 (63)	96 (43)
		—	—	—
		924	548 (59)	312 (34)

TABLE II
Age of Individual and Symptom-Duration
(Percentages in brackets)

Group	Symptom-Duration in Months	All Ages	–45 Years	45–54 Years	55 Years and Over
A	0– 3	187	42 (22)	49 (26)	96 (51)
B	– 6	250	75 (30)	75 (30)	100 (40)
C	–12	262	65 (25)	84 (32)	113 (43)
D	Over 12	225	49 (22)	84 (37)	92 (41)
		924	231 (25)	292 (32)	401 (43)

striking if survival were calculated from the onset of symptoms, and not, as is the case, from the time of treatment. This can only imply that group D is mainly composed of cancers of lower intrinsic malignancy.

It is apparent that survival depends more on the character of the tumour than on the time treatment was given, and few of the women who reported early received the benefit they deserved. Such observations provide no argument against the value of early diagnosis, but they indicate the limitations of educational campaigns based on symptomatology. It is still true that the sooner a patient is treated, the more likely is she to be cured, but the main benefit of educational campaigns will be derived by women with slow growing tumours. Reduction of delay would be most beneficial where it is now longest, and if the women of group D had reported promptly instead of waiting for a year or longer, many more would have received treatment at an early clinical stage, and the overall five-year survival rate of 43 per cent would have been substantially increased.

THE LENGTH OF HISTORY

Cervical cancers have a symptom-free phase of probably variable duration, so the length of history can only be an approximate indication of the age of the disease. The clinical history as recalled by the patient is also notoriously unreliable, but, in spite of these limitations symptom-duration, when correlated with the extent of the disease, may be a valuable guide to the rate of tumour-growth.

The length of history is determined by the intelligence of the patient and by the alertness of her medical advisers, but it is influenced by other factors. A significantly greater proportion of elderly women came early (Table II), and in a small group of 45 women who reported at once, 27 (60 per cent) were 55 years of age or over. Post-menopausal bleeding is more clearly defined, and its potential significance may also be better appreciated by the lay public. In contrast, women of age group 45–54 years, when abnormal haemorrhages are so often ascribed to "natural causes", were much slower in reporting their symptoms (Table II).

It is noteworthy that the average age of women afflicted with the disease has increased in recent years, presumably because there are now more elderly women at risk (Table III). In this survey 43 per cent of the women were 55 years of age or over, compared with 35 per cent in a series previously reported (Maliphant, 1949).

The length of history would also appear to be influenced by the rate of progress of the neoplastic process. It has been noted in cancers

TABLE III
Percentage Distribution of Patients by Age

	–45 Years	45–54 Years	55 Years and Over
1,200 cases seen 1922–1946 ..	30	35	35
924 cases seen 1940–1954 ..	25	32	43

of other sites that the more malignant tumours have the shortest histories, as they seem to cause more alarm than do tumours which change slowly (Balfour, 1937; Bloom, 1950). Women with rapidly growing cervical cancers who delayed for 12 months may have died before reaching hospital, but their number is probably small (Maliphant, 1949), and it seems probable that most of these women sought earlier treatment, and are included in groups A, B or C. Naturally these groups also include many of the more benign types, but their influence on the group survival rates is more than offset by the tumours which are so malignant that, even when taken early, they run a fatal course regardless of therapy.

The main aim of this enquiry was to separate as far as possible the more benign cancers so that their characteristics could be examined, and the cancers of group D would appear to serve this purpose. In spite of a long symptomatic history, 63 per cent of these cancers had still not extended beyond stage 2, and the group as a whole was characterized by relatively good prospects of five-year survival.

The pathological features of the tumours in groups A, B and C were examined independently, but no significant group differences were demonstrable. By contrasting the tumour pathology of the cases in these three groups with those in group D, it was hoped that some light might be shed on the morbid character of "malignancy" as seen in cervical cancer, and that any differences noted would provide data on which to base a more accurate individual prognosis.

Histology

Opinions have differed on the value of histological grading as an index of malignancy, but recent work, notably by Bloom (1950), has again stressed its importance in cancer of the breast.

Microscopic confirmation of the diagnosis was obtained in 886 cases, and the remaining 38 patients (4 per cent) had extensive ulceration of undoubted malignancy. Of the microscopically confirmed cancers 56 (6·3 per cent) were glandular in character, and the 830 epitheliomata were graded on the basis of cell-structure and degree of differentiation into two groups: anaplastic tumours (60·6 per cent) and differentiated tumours (33·3 per cent). In the remaining 6·1 per cent the growths were epidermoid but the biopsy material was unsuitable for reliable microscopic grading. Of the cancers 8·3 per cent were keratinized

Gilmour *et al.* (1949) did not find any difference in the duration of symptoms between the differentiated and anaplastic tumour types, and this has also been our experience (Table IV). Group D contained a significantly greater proportion of glandular cancers, but, in the epitheliomata, no correlation was established between anaplasia and rapid growth.

As slow growing tumours allow more time for their detection while they are still of limited extent, cases first seen with advanced disease

Table IV
Histological Type and Symptom-Duration
(Percentages in brackets)

Groups	Symptom-Duration in Months	Number of Cases Seen	Microscopy Confirmed	Adeno-carcinoma	Epitheliomata		
					Anaplastic	Differentiated	Ungraded
A, B and C	0–12	699	665	32 (4·8)	381 (57·3)	214 (32·2)	38 (5·7)
D ..	Over 12	255	221	24 (11)	122 (55)	62 (28)	13 (6)
		924	886	56 (6·3)	503 (56·7)	276 (31)	51 (6)
Percentage of cases seen in Stages 1 or 2 ..		59		68	62	55	

TABLE V

Distribution of Histological Types in a Group of "Advanced" Cases With Short Histories and a Group of "Early" Cases With Long Histories

(Percentages in brackets)

	Number of Cases	Microscopy Confirmed	Adeno-carcinoma	Epitheliomata			
				Total	Graded	Anaplastic	Differentiated
"Malignant" group	182	167	8 (4·8)	159	150	102 (68)	48 (32)
"Benign" group ..	142	142	21 (14·8)	121	112	84 (75)	28 (25)

include a disproportionate number of the more malignant types. If any correlation exists between anaplasia and rapid growth, relatively more of the anaplastic tumours would be expected to present as advanced lesions, but this was not the case in this series (Table IV). To examine the position further, a comparison is made in Table V of the microscopic findings in 182 "malignant" cases in which the disease had reached clinical stage 3 or 4 with symptom-duration 0–6 months, and 142 "benign" cancers which had not extended beyond stage 2 in spite of a history exceeding 12 months. The only significant difference is again the excess of adenocarcinomata in the "benign" group.

MORPHOLOGY

Eight hundred and thirty-six of the cancers (90 per cent) fell into one of four morphological groups (Table VI). In 436 cases (52 per cent) excavation was the main feature, whereas 284 (34 per cent) presented as exophytic growths. One hundred and sixteen of the tumours (14 per cent) were not conspicuously hypertrophic or ulcerative but caused a barrel-shaped enlargement of the cervix with minimal involvement of the portio. They are grouped as "endocervical" and 14 per cent were adenocarcinomata (Table VII). The incidence of glandular cancers was also high in the exophytic tumours, being almost four times as great in this group as in the ulcerative types (Table VII).

TABLE VI

Morphological Types

(Percentages in brackets)

	Number of Cases	Percentage Seen in Stages 1 or 2
Cauliflower tumour ..	71 (8·5)	67
Hypertrophic plaque ..	213 (25·5)	64
Total exophytic ..	284 (34)	
Ulcerative	436 (52)	53
Endocervical	116 (14)	71
	836	59
Unclassified	88	
All cases	924	59

The ulcers did not differ from the other morphological types in symptom-duration, but relatively fewer were seen at an early clinical stage (Table VI), presumably because they were late in causing symptoms and had a longer symptom-free phase. From the analysis shown in Table VIII, it is evident that there was no correlation between symptom-duration and the morphology of the growth.

DISCUSSION

The failure to recognize any pathological features peculiar to the more favourable cancers of group D may mean that either the pathological criteria employed were inadequate to discriminate "malignancy" in terms of rate of growth, or that the rate of tumour-growth is a function of patient response.

Many known facts about cancer are difficult to explain without the introduction of this factor of patient response. It is well known that malignant cells may lie dormant in the body for long periods, and after many years of quiescence "regain new vigour", but there is

TABLE VII
Correlation of Morphological and Histological Types
(Percentages in brackets)

	All Cases	Microscopy Confirmed	Adeno-carcinoma	Epitheliomata		
				Anaplastic	Differentiated	Ungraded
Exophytic	284	277	25 (9)	150 (54·2)	91 (32·8)	11 (4)
Ulcerative	436	410	11 (2·6)	241 (59)	140 (34)	18 (4·4)
Endocervical	116	114	16 (14)	63 (55·3)	27 (23·7)	8 (7)
Unclassified	88	85	4	49	18	14
	924	886	56 (6·3)	503 (56·7)	276 (31)	51 (6)

TABLE VIII
Morphological Type and Symptom-Duration
(Percentages in brackets)

Groups	Symptom-Duration in Months	All Types	Exophytic	Ulcerative	Endocervical	Unclassified
A, B and C ..	0–12	699	214 (30·6)	326 (46·7)	88 (12·6)	71 (10·1)
D	Over 12	225	70 (31·2)	110 (48·8)	28 (12·4)	17 (7·6)
		924	284 (30·7)	436 (47·2)	116 (12·6)	88 (9·5)

both direct and indirect evidence to suggest that in such episodes the basic alteration has occurred in the host rather than in the neoplastic cell. It is becoming increasingly evident that individuals are capable of controlling or destroying their own tumour cells to a variable degree, and all cancers that disseminate are not necessarily fatal. Recent studies of the fate of cancer cells in the vascular system (Cole *et al.*, 1958; Engell, 1959) and of the behaviour of hormone-dependent tumours have shed new light on the biological nature of host-tumour relationship, and directed further attention to the paramount importance of the bodily defence mechanism against malignant disease.

This section of the survey indicates the limitations of tumour-morphology as a guide to behaviour. The inability to distinguish between rapidly-growing and slow-growing cancers of the cervix may mean that their rate of extension was determined less by qualities inherent in themselves than by the degree of natural resistance offered by their hosts, and it is this "Incomputable Factor in Cancer Prognosis" (Gordon-Taylor, 1959) which makes the outlook for the individual so unpredictable.

The Results of Treatment

Treatment was predominantly radiological and radium was used by a modified Stockholm technique. Eight hundred and ninety-four patients (97 per cent) were treated in this manner, and in 38 of these cases (4·2 per cent) surgery was used as an adjunctive therapeutic procedure. X-irradiation was not employed as a primary form of treatment. In 38 cases (3 per cent) the disease was so extensive that treatment was considered inadvisable. Survival implies survival for five years, and in this section survival rates, which are shown in brackets, are calculated on treated cases only. All cases lost to follow-up (5 per cent) and those dying of incidental disease are regarded as "dead of cancer".

In advanced cases, better results were obtained in the older women, but in general the

TABLE IX
Age of the Patient and Survival
(Percentages in brackets)

Age Group	All Stages				Stages 1 and 2		Stages 3 and 4		
	Seen	Not Treated	Treated	Survivors	Seen and Treated	Survivors	Seen	Treated	Survivors
–45 years ..	231	9	222	86 (39)	141 (61)	76 (54)	90	81	10 (12)
45–54 years ..	292	9	283	88 (31)	174 (59)	76 (43)	118	109	12 (11)
55 years and over	401	12	389	138 (35)	233 (58)	104 (44)	168	156	34 (21)
All ages	924	30	894	312 (35)	548 (59)	256 (46)	376	346	56 (16)

outlook was independent of the *age of the individual* (Table IX). Our findings agree with those of Gilmour *et al.* (1949) in showing no significant difference in the incidence of early growths or in the five-year survival rates in the three age groups studied.

The relation of *Symptom-duration* to survival is shown in Table X. It is a re-statement of Table I adjusted for the clinical extent of the disease.

When corrected for clinical stage, the prognosis is more dependent on the rate of tumour-growth than on any other single factor, and a long history in a growth which is still small is one of the most favourable of all prognostic signs. As previously observed, group D is heavily loaded with cancers of lower growth-potential, and it is in this category of tumour that therapy achieves its main successes. This type of tumour is probably also well represented in the survivors of groups A, B and C, but these groups include most of the rapidly growing cancers which run a fatal course apparently uninfluenced by therapy, and it is this lethal form of the disease which is responsible for the level at which mortality figures of uterine cancer still stand.

Morphology

How far stromal resistance determines not only the rate, but also the mode of extension of the cancer is purely speculative, but it is noteworthy that Macdonald (1951) observed that, if cases with histories exceeding 12 months were still in stages 1 or 2, they proved almost invariably to be exophytic growths. We have not confirmed this, but it has been previously noted that, irrespective of the clinical stage of the disease, the ulcerative, destructive cancers are lethal, while the exophytic types are associated

TABLE X
Symptom-Duration and Survival
(Percentages in brackets)

Symptom-Duration in Months	All Stages				Stages 1 and 2		Stages 3 and 4		
	Seen	Not Treated	Treated	Survivors	Treated	Survivors	Seen	Treated	Survivors
0– 3	187	9	178	64 (36)	116	56 (48)	71	62	8 (13)
– 6	250	9	241	73 (30)	139	59 (42)	111	102	14 (14)
–12	262	7	255	79 (31)	151	64 (42)	111	104	15 (14)
Over 12	225	5	220	96 (44)	142	77 (54)	83	78	19 (24)
	924	30	894	312 (35)	548	256 (46)	376	346	56 (16)

TABLE XI
Morphological Type and Survival
(Percentages in brackets)

Type	All Stages			Stages 1 and 2	
	Seen	Treated	Survivors	Treated	Survivors
Exophytic	284	279	105 (37·6)	184	91 (50)
Ulcerative	436	415	117 (28)	233	89 (38)
All cases	924	894	312 (35)	548	256 (46)

TABLE XII
Morphological Type and Survival Corrected for Symptom-Duration
(Percentages in brackets)

Symptom-Duration in Months		All Stages		Stages 1 and 2	
		Treated	Survivors	Treated	Survivors
0–12	Exophytic	211	72 (34)	134	61 (45)
	Ulcerative	309	77 (25)	171	60 (35)
	All cases	674	216 (32)	406	179 (44)
Over 12	Exophytic	68	33 (48)	50	30 (60)
	Ulcerative	106	40 (38)	62	29 (47)
	All cases	220	96 (44)	142	77 (54)

with better survival rates (Maliphant, 1947). This is again shown in Table XI, and after correction for symptom-duration in Table XII.

Histology

Since the group of slow growing cancers did not differ significantly from the others in their microscopic features, "histological malignancy" would not be expected to affect the outcome, unless the anaplastic tumours were more responsive to radiation. In previous surveys, when the epitheliomata were graded into "spinal", "transitional" and "spindle" cell types, no significant differences were noted in the survival rates, though slight variations were observed in favour of the anaplastic tumours (Maliphant, 1933, 1947). Glücksmann (1948), on the contrary, found significantly better

TABLE XIII
Histological Type and Survival
(Percentages in brackets)

	All Stages			Stages 1 and 2		Stages 3 and 4		
	Seen	Treated	Survivors	Treated	Survivors	Seen	Treated	Survivors
Epithelioma:								
Anaplastic ..	503	497	175 (35)	312	144 (46)	191	185	31 (11)
Differentiated ..	276	269	86 (32)	152	66 (45)	124	117	20 (17)
Ungraded ..	51	48	24	34	22	17	14	2
Adenocarcinoma ..	56	56	22 (39)	38	19 (50)	18	18	3 (16)
No histology ..	38	24	5	12	5	26	12	0
	924	894	312 (35)	548	256 (46)	376	346	56 (16)

TABLE XIV

Histological Type and Survival (Corrected for Symptom-Duration)

(Percentages in brackets)

	All Cases			Duration of Symptoms					
				0–12 Months			Over 12 Months		
	Seen	Treated	Survivors	Seen	Treated	Survivors	Seen	Treated	Survivors
Epithelioma:									
Anaplastic ..	503	497	175 (35)	381	379	118 (31)	122	118	57 (48)
Differentiated	276	269	86 (32)	214	208	68 (33)	62	61	18 (30)
Adenocarcinoma	56	56	22 (39)	32	32	9 (28)	24	24	13 (54)
All Cases ..	924	894	312 (35)	699	674	216 (32)	225	220	96 (44)

TABLE XV

Histological Type and Survival

(Exophytic and Ulcerative Growths Considered Separately)

(Percentages in brackets)

	Exophytic Growths		Ulcerative Growths	
	Treated	Survivors	Treated	Survivors
Epithelioma:				
Anaplastic	149	53 (36)	238	70 (30)
Differentiated	90	38 (42)	137	34 (25)
Adenocarcinoma	25	10 (40)	11	4 (33)
All cases	279	105 (37·6)	415	117 (28)

survival rates in patients with differentiating tumours than in those with anaplastic types.

In women with histories exceeding 12 months, survival in the differentiating tumours was below average (Table XIV), but in general we have again failed to establish any real difference in the survival rates of the anaplastic and differentiating tumours for any stage or for all stages combined (Table XIII). Neither could any correlation between histological type and survival be shown when the exophytic and ulcerative growths were considered separately (Table XV).

It does not seem therefore that histological grading based on the degree of anaplasia materially affects the outcome in radiologically treated cancer of the cervix and this also applies to long term survival. When the distribution of histological types is examined in patients who have survived 5, 10 and 20 years, the ratio of anaplastic to differentiating tumours remains substantially the same in all groups (Table XVI).

SUMMARY

Cancers of the uterine cervix present in many different lethal forms, and, by grouping the cases according to symptom-duration, some segregation is effected of the less malignant types.

Survival after radium was not significantly affected by the age of the individual or by the histological grade of the tumour. The outlook was determined almost exclusively by two

TABLE XVI

Ratio of Anaplastic and Differentiating Tumours in Graded Epitheliomata of the Cervix
(Percentages in brackets)

	Before Treatment		Survivors Following Radium Treatment		
	Gilmour (1949)	Cardiff	5 Years	10 Years	20 Years
Anaplastic	627 (63)	503 (64)	431 (64)	139 (66)	53 (72)
Differentiating	365	276	246	71	20
	992	779	677	210	73

factors: the rate of tumour-growth and the extent of the disease when first seen.

Therapy achieves its best results in the cancers which grow relatively slowly. These more favourable tumours did not present any distinctive pathology and the results of this investigation are consistent with the view that the slow growing cancers are seen in women who possess a high degree of natural resistance to the disease.

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THE RECTO-VESICAL LIGAMENT IN ASSOCIATION WITH DOUBLE UTERUS*

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PROFESSOR Carl Gustav Carus of Dresden briefly referred to the recto-vesical ligament in his interesting textbook of midwifery written in 1824 but the ligament was not mentioned by Eisenmann in the review of the literature published with his anatomical tables of double uterus in 1752. However, as double uterus was recognized as early as 1557 by Francois Cotti (Ombredanne and Martin, 1903), it seemed unlikely that the ligament could have passed unnoticed until the nineteenth century. Secheyron in 1885 reproduced an engraving, probably from a post-mortem specimen, which clearly illustrated this fold. The print was taken from a book *Instruction utile et familière aux Sage-Femmes* written by Madame de Lamarche of Paris in 1710 and this is the earliest record of the ligament I have been able to trace.

ANATOMY

The recto-vesical ligament (Fig. 1) is a double peritoneal fold with a free superior margin extending in the sagittal plane from the anti-mesenteric border of the lower large intestine to the posterior wall of the bladder. Its depth, width and substance are inconstant and, to the best of my knowledge, it is found only in association with double uterus cleft externally to or through the level of the internal cervical os.

The posterior segment may arise from the bowel at any level between the upper sigmoid colon and the second part of the rectum. It sweeps forwards as a falciform partition dividing the pouch of Douglas into two recesses, approximately of equal size and normal depth, to the angle of the split uterus. The partition may be between 1 and 4 mm. in thickness near its upper margin and somewhat thicker at its base. In some cases this recto-uterine segment may be absent and the anterior rectal wall may be advanced to the saddle of the uterus where it may come into contact with the posterior bladder wall. In other cases the upper margin of the septum may arise from the anti-mesenteric surface of the sigmoid colon at a high level and sweep downwards and forwards for 9 inches or more to the uterine cleft as a thin, double, peritoneal fold with a sharp upper margin and a structure and appearance similar to that of an intestinal mesentery (Fig. 2). In the majority of cases, however, an intermediate stage between these extremes is found.

After crossing the uterine bifurcation as a median ridge covered by peritoneum the ligament passes forwards on to the posterior bladder wall, largely obliterating the medial part of the utero-vesical pouch of peritoneum. It may merge imperceptibly into the bladder wall or it may continue as a single or double peritoneal fold for a lesser or greater distance over the bladder and, in exceptional cases, may reach and join the median umbilical fold as it

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extends up towards the umbilicus. In general the anterior utero-vesical segment is shorter than the posterior recto-uterine segment.

Between the layers of the peritoneal fold is a well-marked band of connective tissue which may be looser near the rectal wall and more condensed over the uterus (Fig. 3). Histologically smooth muscle fibres are seen in a fibrillary connective tissue frame-work and anastomotic branches between the intestinal and vesical vessels may sometimes be demonstrated (Rodi, 1929). On occasion a little fat may be seen in the posterior segment.

To the naked eye in some cases no vessels are visible yet in others comparatively large vessels pass forwards in the ligament towards the bladder. These larger vessels seem to originate from the confluence of multiple small vessels, presumably derived from the haemorrhoidal arterioles, on the anterior surface of the rectum. After crossing the uterus they soon ramify over the posterior bladder wall and are lost to view. Veins are usually small, relatively inconspicuous and few in number. When the ligament has a high origin from the sigmoid colon and is extensive, arterial arcades may form 1 or 2 centimetres from the anti-mesenteric border of the colon and connecting links between branches of the superior haemorrhoidal artery and the arterial arcades may readily be demonstrated. The main vessels from these arcades may cross the uterine bifurcation or may continue down the anterior rectal wall to be lost to view when the ligament reaches the base of the pouch of Douglas.

Aetiology

Many attempts have been made to explain the origin of this ligament and the associated uterine deformity. Some authors state that the uterine deformity and others that the ligament itself is the primary defect. Among the many suggested causes are non-infective foetal meconium peritonitis following bowel rupture due to intestinal stenosis or adhesion to the umbilical ring; megacolon, volvulus, intussusception or Meckel's diverticulum; bladder over-distension and rupture, tension on the body stalk and umbilical cord, bunching of the allantois on the developing bladder and delayed union of the pubes. It has been suggested that pelvic peritoneum will naturally fall into folds when draped over a double uterus or that interposition of myomatous cell rests, of abnormal umbilical vessels or branches of the haemorrhoidal vessels between the Müllerian ducts, traction on short round ligaments or transposition of the lower mesonephric and paramesonephric ducts may be responsible for the malformation.

Most of these theories are inadmissible because the suggested cause would not operate until after the union of the paramesonephric ducts, because the ligament has a definite anatomical structure or because the ligament is not present in cases of lesser uterine fusion deformities. To me the explanation which seems most convincing is that the primary cause of the ligament is an error of cloacal development which gives rise to an irregular connexion between the bladder and terminal bowel. This may be associated with persistence of a vesical branch of the superior haemorrhoidal artery and possibly of a remnant of the ventral mesentery analogous with the falciform ligament of the liver or gastro-hepatic omentum.

The Cloaca

In the developing ovum, after the embryonic plate has been infolded to form the primitive gut, the hind-gut dilates to form the cloaca from which the allantoic and caudal diverticula arise. At about 5 mm. crown rump length a crescentric mesenchymal wedge, the coronal uro-rectal septum, develops in the cranial angle of the cloaca and, advancing the cloacal epithelium before it, grows caudally and medially towards the imperforate cloacal membrane. By this means the urogenital and allantoic compartment is progressively partitioned from the rectal canal. At 8 mm. these cavities communicate only by a narrowing cloacal duct and at 16 mm. the septum fuses with the cloacal membrane and the partition is complete. As the urogenital compartment migrates ventrally and the rectal compartment dorsally the interposed bridge of mesenchyme is attenuated and depressed.

FIG. 1

Recto-vesical ligament. The ligament, associated with uterus bicornis bicorpus bicollis (Hunter, 1950), is typical of that found in the majority of cases of double uterus.

FIG. 3

Recto-vesical ligament. The gross structure of the ligament and the merging of its connective tissue with the subjacent myometrium is illustrated (following hysterectomy).

FIG. 2

Sigmoid-vesical ligament. The posterior segment of the ligament is long and associated with uterus bicornis bicorpus bicollis (following Caesarean section—uterus turned forwards).

If the cloacal duct fails to close a recto-vesical fistula will occur. If the epithelium of the urogenital compartment retains its attachment to that of the rectum at the site of the closed cloacal duct the bladder wall will retain its intimate contact with that of the rectum. If the attachment is of a looser nature the walls of the two viscera will be connected by a mesenchymal and later by a fibromuscular band.

The Paramesonephric Ducts

In the early somite stage of the embryo the intra-embryonic mesoderm on either side of the neural canal develops into the paraxial segmental somites, the lateral mesodermal plate adjoining the recently-formed coelomic cavity and, between these regions, the intermediate cell mass. At the 10 somite stage pronephric buds appear in the cephalad extremity of the intermediate cell mass on either side and the pronephric duct is formed by union of the primitive duct segments, extends in a caudad direction as more somites are formed and gains attachment to the presumptive urogenital region of the cloaca at 4 mm. C.R. length (25 somite stage). At about 3 mm. C.R. length the mesonephric vesicles first appear and gain attachment to the pronephric—now the mesonephric—duct. At 5 mm. the functionless pronephros has degenerated.

At 10 mm. C.R. length the paramesonephric duct on either side arises as a bud of cells from the coelomic mesoderm immediately above the highest mesonephric vesicle on the developing urogenital ridge. It grows as a solid column of cells in close juxtaposition with the mesonephric duct which it follows intimately in a caudad direction. It later becomes vacuolated and canalized from above downwards and, as it separates from the mesonephric duct, takes up a distal position in the attenuated urogenital fold. As the two urogenital folds approximate at the narrowing base of the coelom they pass medially through the mesodermal septum transversum. The two paramesonephric ducts are then brought together and run side by side, medial to the mesonephric ducts, through the genital cords to fuse with the urogenital compartment of the cloaca. Later they unite to form the elementary endometrium and vaginal bud. Condensations of the enveloping mesenchyme ultimately form the myometrium and the round and broad ligaments.

If the caudad extension of the mesonephric duct is arrested the paramesonephric duct will not develop beyond the point of interruption and a contralateral unicornuate uterus with absence of the kidney of the same side will result. If the growth of one paramesonephric duct is temporarily delayed it will reach the midline in the septum transversum after that of the opposite side, fusion between the two ducts will probably be incomplete and a septate uterus may result. If the two paramesonephric ducts are kept apart in the genital cords by "traction" of short round ligaments, incomplete development of the septum transversum, or interposition between the ducts of mesenchyme, blood vessels, mesonephric ducts, rectum or bladder, the paramesonephric ducts may fail to unite and bicornuate uterus may result.

Vascular System

If we study the development of the vascular system we find that the early paired aortae, later fusing to form the conjoined aorta, give rise to dorsal, lateral and ventral intersegmental branches. The dorsal arteries supply the body wall, the lateral arteries chiefly the genital ridge and the ventral arteries the gut and yolk-sac. As the gut is delimited from the yolk-sac it acquires a dorsal and, for a short time, a ventral mesentery. At this stage the paired ventral arteries are brought together and fuse forming, among others, the coeliac and mesenteric arteries. The iliac arteries and their branches, including the allantoic and umbilical arteries, remain paired. A free anastomosis takes place in the omphalo-mesenteric arterial system and the venous system conforms with a similar pattern.

If an arterial link persists between the blood vessels of the terminal bowel and the bladder this may be associated with or may lead to persistence of the ventral mesentery in the pelvic region. This persistent fold may become the recto-vesical ligament and, with its contained blood vessels, may hinder union of the

para-mesonephric ducts. The vascular link may be more likely to persist if there is an irregular connexion between the bladder and rectum.

It therefore seems probable that the chief factors concerned with the production of a deeply cleft uterus associated with recto-vesical ligament are failure of complete separation of the rectum from the bladder base, persistence of the embryonic recto-vesical vascular anastomosis and failure of normal approximation and union of the two paramesonephric ducts to form a single endometrial cavity.

Clinical Importance

It may be said that the recto-vesical ligament is of relatively little consequence in practical gynaecology and obstetrics. In the non-pregnant state its chief importance rests with the distortion of anatomical relationships encountered during hysterectomy in cases of major uterine deformity. Difficulty may then be experienced in freeing the bladder and utero-vesical ligament from the anterior aspect of the uterus without damaging the bladder wall, particularly when the ligament is short and the bladder and rectum are approximated to one another across the uterine saddle. Under similar circumstances, but to a lesser degree, there is a risk of damaging the rectal wall during separation from the posterior aspect of the uterus. The division of the septum should therefore be carried out at an early stage of the operation, usually immediately after dividing the round ligaments. Victor Bonney (1952) has stressed the importance of pushing the bladder well forwards and the rectum well back from the uterus after the septum has been divided during the course of hysterectomy.

In the obstetrical case similar difficulty may be met during lower segment Caesarean section and the operation may be further complicated by increased vascularity of the ligament and of the softened vesical and rectal walls (Hunter, 1957). Sloan (1958) described a case of obstructed labour due to impaction and incarceration of the non-pregnant horn of a deeply cleft double uterus beneath a recto-vesical septum.

Summary

The anatomy of the recto-vesical ligament is described, its aetiology and embryology are discussed and its practical importance is outlined.

I am indebted to Drs. M. Caturani and J. Lederer who have given invaluable assistance by translating articles from the foreign press.

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SUCCESSFUL PREGNANCY FOLLOWING TREATMENT FOR PELVIC TUBERCULOSIS

BY

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RECOVERY from female genital tuberculosis without inevitable loss of reproductive function has been made possible by current therapy. Numbers of records of pregnancy subsequent to treatment have now been published (Donaldson, 1952; Stallworthy, 1952; Rabau, 1952; Sutherland, 1952; Barns *et al.*, 1953; Bromberg and Rozin, 1954; Earn, 1958) but the majority of pregnancies have been unsuccessful either because of tubal implantation or because of miscarriage of an intra-uterine pregnancy. The case history is presented of a patient delivered of two full-term living infants after treatment for genital tuberculosis.

Mrs. M.S., a primigravida aged 20 years, was admitted to the gynaecological ward of St. James's Hospital, Leeds, on 23rd April, 1953. The patient complained of lower abdominal pains present for 2 days, now becoming rhythmical, and of vaginal bleeding present for 12 hours. The last menstrual period had occurred 6 months previously and foetal movements had been felt for a month. There was no relevant medical history.

On examination the patient appeared well nourished and of normal colour and hydration. No abnormality was detected in the cardiovascular or respiratory systems. The uterine fundus could be felt arising 1 finger's breadth above the upper margin of the umbilicus. The uterus was contracting in time with the pains and it was evident that abortion was inevitable.

The next day cervical dilatation had occurred. The patient's temperature was 104·5° F. and the uterus was tender on palpation. Treatment was instituted with intramuscular injections of 500,000 units of soluble penicillin and 0·5 g. of streptomycin sulphate twice daily. In the evening a male foetus 11½ inches (29 cm.) long was passed weighing 1 pound 2 ounces (512 g.). The placenta followed spontaneously and appeared complete. No pathogenic bacteria were grown from a vaginal swab sent that day.

Four days later the patient had a small vaginal haemorrhage and a piece of placenta was passed. The uterus was noted to be markedly tender. Digital evacuation of the uterus was performed under general anaesthesia; amorphous debris, only, was retrieved. The pyrexia persisted and a further vaginal swab grew *Staphylococcus albus* coagulase positive, declared sensitive to aureomycin. This antibiotic was administered in the dosage of 250 mg. orally 6-hourly but the fever did not resolve.

Nineteen days after the abortion with pyrexia still sustained and with rigors occurring from time to time, abnormal physical signs developed in the pelvis. A mass could be felt on the right displacing the uterus to the left and this was assessed to be a pyosalpinx. It was observed that the leucocyte count was low.

Laparotomy was performed on the following day through a left lower paramedian incision. The parietal peritoneum was seen to be markedly thick and oedematous whilst the greater omentum adhered to it diffusely. In the pelvis countless pin-head sized tubercles were scattered over both visceral and parietal peritoneum. The right Fallopian tube proved to be an adherent caseating mass, it was therefore excised. The left tube, though grossly oedematous and covered with tubercles, showed no distension to suggest contained pus. It was considered reasonable to conserve this tube. The appendix, being acutely inflamed, was also removed.

The tube and appendix were sent for histo-

logical and bacteriological study. Both organs were reported to be the site of caseating tuberculosis and from the tube a growth of *Mycobacterium tuberculosis* was cultured.

Following operation treatment was continued with intramuscular injections of 0·5 g. of streptomycin sulphate twice daily and oral administration of para-amino-salicylic acid was added commencing with a dose of 3 g. three times daily. The patient appeared to make good progress at first but 17 days after operation she complained of pain in the left leg and calf tenderness could be elicited. A left femoral vein thrombosis developed; under the influence of anti-coagulant therapy the condition progressively improved.

Two weeks later severe frontal headache was experienced; neck stiffness and a positive Kernig's sign were present. At lumbar puncture the manometric pressure of the cerebrospinal fluid was found to be 240 mm. of water. Thirty-nine polymorphonuclear leucocytes and 59 lymphocytes were present per c.mm. The protein was raised to 100 mg. per cent while the sugar was lowered to 23 mg. per cent and the chlorides to 645 mg. per cent. Subsequent culture showed the presence of the *Myco. tuberculosis*. The patient was transferred to the Infectious Diseases Hospital for treatment of her tuberculous meningitis.

At Seacroft Isolation Hospital 100 mg. of intrathecal streptomycin sulphate was given daily for 3 months then 3 times per week for a further 3 months. For the whole of this 6 months 1 g. of streptomycin sulphate was given twice daily intramuscularly. In addition 25 g. of para-amino-salicylic acid and 300 mg. of isonicotinic acid hydrazide were administered orally each day. The pyrexia persisted for 3 months and the patient had amenorrhoea for 5 months.

In February, 1954, 8 months after admission to the Isolation Hospital, Mrs. M.S. was discharged. Follow-up examinations in November, 1954 and November, 1955 confirmed that the patient remained in good health with no residual disability. The cerebrospinal fluid on each occasion had a normal chemistry and cytology.

On 23rd April, 1956, the patient visited the antenatal clinic stating that she had not experienced a period since 7th March.

Examination revealed that the uterus was enlarged and the organ had the characteristic cystic consistency of early pregnancy. Pregnancy was subsequently confirmed and, apart from 7 days in-patient treatment for threatened abortion in August, gestation progressed uneventfully. In December the patient had a normal delivery of a full-term living female infant weighing 6 pounds 5 ounces.

The puerperium was normal and the patient left the midwifery unit on the 10th day. On postnatal examination 6 weeks after confinement she was found to be in good health, no abnormality being felt either on abdominal or on vaginal examination.

In December, 1958, Mrs. M.S. again had a normal confinement following an uneventful pregnancy, giving birth to a living male infant weighing 7 pounds 7 ounces.

Accounts of treatment by various authorities (Stallworthy, 1952; Rydén, 1953; Sutherland, 1957) where pelvic tuberculosis alone has been the problem, indicate a lesser dosage and duration of treatment than was administered in this case. Three and 4 month regimes of streptomycin sulphate 1 g. daily intramuscularly have been commonly used along with para-amino salicylic acid 20 g. with or without the addition of isonicotinic acid hydrazide 100–300 mg. daily. In this instance 2 g. of streptomycin sulphate were given each day for 6 months along with 25 g. of para-amino salicylic acid and 300 mg. isonicotinic acid hydrazide. It is possible that this heavy schedule of dosage was responsible for the astonishingly successful outcome.

I am grateful to Mr. H. Agar, under whose care this patient was managed and who performed the laparotomy, for permission to record this case history. I also pay tribute to Miss Hester de C. Woodcock, Consultant in Infectious Diseases, for her expert management of the complication of tuberculous meningitis.

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THE PLACENTA, ITS CIRCULATION AND LOCALIZATION

BY

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INTRODUCTION

WITH the introduction of arterial catheterization by Seldinger (1953) many of the limitations to arteriography were removed.

Shortly after this apparatus was first used in King Edward VIII Hospital, it was felt that localizing a placenta by its circulation could possibly fall within the compass of a routine radiological procedure. The method used in the first 25 cases has been described in a preliminary report by de Villiers and Brink (1957). A progress report was made at the South African Medical Congress by the author in October, 1957.

After a slow start placentography has become firmly established as a reliable method of placental localization in this hospital. In addition it has proved to be valuable in the assessment of placental circulation and other anomalies.

Almost 200 cases have been examined. No ill-effects on the mother or foetus could be ascribed to the procedure.

TECHNIQUE

The Seldinger apparatus, apart from the polythene tubing, is autoclaved in a drum with towels, syringes, two receiving bowls and a selection of needles.

The polythene tubing is sterilized by placing it in long glass tubes filled with Zephiran 1 in 1,000. This keeps the catheter straight and easy to handle.

The examination is performed under local anaesthesia, 30 minutes after the subcutaneous administration of 100 mg. of pethidine.

The femoral artery is punctured just below the inguinal ligament. A small nick is made in the skin at the proposed puncture site. This is done to avoid damage to the tip of the catheter as it passes through the skin.

In puncturing the artery it should be transfixed, i.e., the needle is passed through the anterior and posterior walls of the vessel. The needle is then removed, and the blunt cannula slowly withdrawn with the base depressed. This flexes the anterior wall and stretches the posterior wall of the artery. As the end of the cannula comes through the posterior wall, its release causes a distinct click and the blood spurts out. The soft end of the guide wire is passed through the cannula into the femoral artery and the cannula removed. The polythene catheter is fed over the guide wire up to the skin and then both catheter and guide wire are simultaneously passed up the femoral artery.

The method of puncturing the artery by transfixing it is advocated, as it is virtually impossible for the needle tip to lie between the layers of the arterial wall and thus cause a dissecting aneurysm.

A linen measuring tape is included in the sterile drum to measure the catheter before use. It is then easy to ascertain when 9 inches of catheter have been passed up the aorta.

The technique is surprisingly simple, and newcomers to this department have managed it at the first attempt.

To avoid unnecessary radiation the author established that the aortic bifurcation is between 7 and 9 inches from the site of the femoral puncture. At 9 inches the tip of the catheter is still well below the renal artery. The importance

of this is that, if the catheter is placed directly opposite and facing into one renal artery, a large dose of contrast medium delivered rapidly may cause severe renal damage.

With the catheter in position the patient is turned into the lateral position. The upper leg is extended and the lower leg flexed. This position, 5° off lateral, is preferred as it opens up the pelvis and permits better visualization of the low-lying placenta. A bucky binder is applied to steady the patient and a wedge filter fitted to the tube. The lateral position is used as it has been found that most placentas were on the anterior or posterior wall, and in this position a *profile view* of the placenta was obtained. This is preferable to the "en face" view for accurate localization of the placental margins.

The contrast medium used for the first 25 cases was 50 per cent Diagonal, the next 75 cases 50 per cent Hypaque, and the remainder 76 per cent Urografin.

Diagonal produced a far greater degree of discomfort than Hypaque or Urografin. Urografin 76 per cent, despite its higher concentration, is the blandest of these media, gives good pictures, and has virtually no side-effects. Its one disadvantage is its viscosity. This is overcome by warming it to just above body temperature. Twenty ml. of contrast medium are injected as rapidly as possible manually and a film is taken 2 seconds after the completion of the injection as timed on a stop watch. In 80 per cent of cases this is sufficient. If the placenta is low-lying the patient is now turned on her back, and the injection repeated with a film taken in the A.P. projection. This is to assess the downward extension in two planes and to establish the degree of placenta praevia present. In the vast majority of cases the investigation is completed in 20 minutes with no real discomfort to the patient.

In 8 per cent of cases the placenta is poorly visualized in the film taken at 2 seconds. If contrast medium is still visible in the uterine and gluteal arteries the next film after re-injection is taken with a 3 second delay. If complete arterial clearing is seen in the first film, a repeat is timed at 1 second. It is very rare to find complete clearing at 2 seconds, while a slow circulation time is relatively common.

Material

Of the 209 cases examined, the first 25 cases have been reported (de Villiers and Brink, 1957). Since then the procedure has been standardized and the last 184 cases have been analyzed. Ante-partum haemorrhage was the indication for placentography in 174 cases. Of the remaining patients 8 were cases of known foetal death, 2 with extra-uterine pregnancies.

A. Cases of Ante-partum Haemorrhage

Among the cases of ante-partum haemorrhage 34 were found to be due to placenta praevia. These were classified as:

	Cases
Type I	19
Type II	9
Types III and IV	6
Total	34

The placentas situated in the upper segment when classified as to their implantation site were as follows:

Mainly anterior wall ..	69
Mainly posterior wall ..	56
Mainly lateral walls ..	14
	139

The remaining case was one of a hydatidiform mole.

In this series the pattern of placental circulation varied considerably and when placental insufficiency was successfully diagnosed for the first time it was decided to investigate the placental circulation in cases of known foetal death.

Cases of Known Foetal Death

Cases of known foetal death examined are divided into two groups:

Group 1: Placental Shut-down (5 cases)

There were 5 cases of complete shut-down, 1 within 8 hours of foetal death. In all these cases only the odd sinusoid was shown, but in 2 of them the uterine arteries demonstrated the placental site well. In all of them the placental position was easily assessed by these arteries.

FIG. 1

A normal placentogram situated posteriorly in the fundus. This illustration demonstrates the typical "star-like" sinusoids.

FIG. 2

A central placenta praevia as demonstrated in the lateral view.

D.B.

FIG. 3

Same case showing the placenta extending right across the internal os of the cervix.

FIG. 4

The placenta is shown on the anterior uterine wall. Its circulation is unimpaired but the foetus is dead. Note the Spalding's sign in the foetal skull in a breech presentation.

D.B.

FIG. 5

This placenta shows only one group of functioning sinusoids situated in the fundus posteriorly. The foetus was alive at the time of examination, but died *in utero* some 3 weeks later (see text).

FIG. 6

Early pregnancy with placenta situated anteriorly in the uterine fundus. A large fibroid has indented the placental surface, giving its outer aspect a concave curve.

FIG. 7

This film is taken 7 seconds after the completion of the injection and illustrates the severe spasm sometimes encountered in the toxaemic states. The arteries are still clearly visualized in this picture.

FIG. 8

Placenta membranacea. Placental sinusoids are seen scattered over the entire anterior aspect of the uterus and a similar picture was obtained in the lateral projection.

Group 2: Placenta Still Circulating (3 Cases)

This group comprised 3 cases, one examined within 24 hours, another at about 48 hours after foetal death. The most interesting one was a case with a positive Spalding's sign with the foetus known to be dead for 2 weeks. The placenta showed unimpaired circulation (Fig. 4).

Discussion

A. Localization

Although this examination has proved to be a completely safe and reliable method of placental localization, it must be stressed that it has no place in the massive exsanguinating haemorrhage requiring operative intervention.

Its main function is in the early haemorrhage between 28- and 32-weeks pregnancy. A placenta praevia is diagnosed or excluded with complete certainty regardless of the duration of pregnancy or the placental type, e.g., a placenta membranacea. In this series there were 2 cases of placenta membranacea.

The exclusion of a placenta praevia saves many a hospital bed and the patient and doctor unnecessary anxiety. At this hospital it has an added importance, because many of the patients on discharge return to their kraals in the native areas remote from even rudimentary medical aid. Macafee (1956) has pointed out that the foetal mortality in the cases of ante-partum haemorrhage who are discharged is 27·3 per cent. Perhaps placental insufficiency and concealed accidental haemorrhage play a part in these foetal deaths, and a vascular assessment of the placenta may well reduce this figure considerably.

In placental localization arbitrary levels have been selected as the site of commencement of the lower uterine segment and of the cervix of the uterus.

If a placenta extended below the anterior superior iliac spine anteriorly, or reached the level of the first sacral segment posteriorly, it was considered as encroaching on the lower uterine segment, that is a type I placenta praevia. If it reached the level of the ischial spines it was considered to have reached the internal os of the cervix.

Perhaps further observations on a bigger series will result in acceptable surface or bony markings for the borders of the various types of placenta praevia. This would remove the only difficulty attendant on placental localization by this method. It is submitted that this difficulty has only arisen in consequence of the accuracy available with arterial placentography. Clear visualization now makes it possible to separate the various degrees of placenta praevia. Recently Samuelsson and Sjövall (1957) put a clip on the uterine cervix and measured the distance between the clip and the placental edge. In a very small series they postulated that, if the placental edge was within 10 cm. of the clip, it probably encroached on the lower uterine segment.

The figures of the placenta in its various positions are self-explanatory. There is a certain degree of variation in the vascularity of the placenta depending on its implantation site; the fundal placenta tends to be thicker and show up much better than the low implantation. The placenta praevia is often thinner and covers a larger surface area. Apart from this variation there are cases which show a relatively poor circulation regardless of implantation site, and it is here that only further experience will make it possible to assess what degree of circulatory impairment will cause foetal death or impede foetal growth.

It is as well to sound a note of warning here as a single film taken at 2 seconds may produce a relatively poor picture, because it has been found that in about 5 per cent of cases the circulation is either slow or fast. If the uterine arteries are still visible, and good placental sinusoids have not been demonstrated a further film should be taken at 3 seconds or even later. Only when a slow circulation has been excluded is it possible to attempt to assess placental insufficiency.

Since the completion of this series the author has done several examinations on European patients in private radiological practice. In the very small series done on this ethnic group it is a startling feature that the filling of sinusoids appears to occur appreciably later and a film taken at 3–4 seconds is probably the best.

B. Assessment of Circulation

As the series has grown, it has become obvious that placental localization is but a part of the information that can be gleaned from arterial placentography. Placental circulation and insufficiency have played an increasingly prominent part in this examination. It was brought to the fore by a case which showed only two placental sinusoids in the fundus (Fig. 5).

The patient was an African female aged 18 years, a primigravida who presented with a painless haemorrhage. She was not anaemic and the period of gestation was assessed at 32 weeks. The haemorrhage continued but was not severe and the foetal heart was normal. A week later the patient was submitted to placentography. The examination showed only two placental sinusoids situated in the upper segment of the uterus. At first report this was considered to be a case of foetal death, but when the clinician reported that the foetal heart was clearly heard, this was amended to one of placental insufficiency, and a firm prognosis made that this foetus would not survive to term. On discharge there had been no haemorrhage for some time and the foetal heart was charted as being loud and clear.

One month later she returned with a recurrence of haemorrhage, small in amount which stopped spontaneously. She went into labour and was delivered of a macerated foetus weighing 3 pounds 2 ounces.

This opened up a new line of thought and 8 cases were investigated in which foetal death was known to have occurred clinically. Some of these showed placental shut-down within 24 hours while others (notably seen in Figure 4) showed a very adequate placental circulation with a foetus showing a definite Spalding's sign, and known to be dead for 10 days. This is taken as a graphic indication that foetal death may be due to

(*a*) primary foetal causes, or
(*b*) secondary to insufficient placental circulation.

It is unfortunate that it has been impossible to investigate further the living foetus with placental insufficiency in this hospital. The vast majority of the deliveries performed are on patients who have never attended the antenatal clinic; a very small proportion attend the clinic *regularly*. This makes the clinical assessment of placental insufficiency well nigh impossible and the cases we have encountered have been purely fortuitous and associated with ante-partum haemorrhage. Perhaps other institutions with a different type of patient, who attends clinic regularly, will be able to pursue this investigation further.

It must be stressed here that the placental site may be obvious due to the leash of uterine arteries marking the implantation site, but only the demonstration of the "star-like" sinusoids indicates a functioning placenta. These arteries diminish considerably with placental shut-down, but can still be seen marking the implantation site several days or even weeks later. It is in these cases that the film timed at 2 seconds usually shows a complete clearance of the contrast medium. Perhaps this is due to the fact that, as blood is no longer circulating through the placenta, it is drained away more rapidly by the uterine veins.

As the technique of examination has improved with experience retroplacental clots have been diagnosed correctly with increasing frequency. These are seen as an interruption in the placental sinusoids, or a loss of parallelism between the placenta and the uterine wall. The latter appearance may be simulated by a fibroid as shown in Figure 6.

Another type of placental insufficiency is that due to spasm as seen in severe toxaemias. This is graphically illustrated in Figure 7.

The patient, an African female aged 30 years, para-7, presented at hospital with vaginal bleeding for 24 hours. It came in spurts accompanied by pain. Her blood pressure was 120/100, she was slightly oedematous, not anaemic and her gestation was assessed at 36 weeks. The following day her blood pressure was 160/110 and a placentogram was requested. She was in labour at the time, having mild uterine contractions. The placentogram showed marked spasm of the uterine lumbar and renal arteries, the contrast medium being still visible 7 seconds after the completion of the injection. This is a remarkable degree of spasm, and the only area in which hold-up of this order is occasionally seen is in the limb arteries, which appear to be more liable to spasm than others. Even in gross malignant hypertension, while spasm has been noted, it has never been seen as severe as this. No contrast medium could be seen in the placental circulation. She was delivered of a live baby weighing 4 pounds eight hours later.

This opens yet another field of investigation which the author hopes to pursue. The behaviour of the placental circulation after foetal death, particularly in those cases in which toxaemic symptoms persist, may throw some light on the aetiology of the toxaemias of pregnancy. If

some of the theories are to be accepted, then the circulation of the placenta in these cases must persist after foetal death, while in those in which the toxaemic symptoms disappear it is expected that the spasm will have disappeared, and the placenta will have shut down. This concept is supported by one case in which the symptoms of pre-eclamptic toxaemia diminished markedly after foetal death, and a subsequent placentogram showed no vascular spasm, and virtually complete placental shut-down.

Browne and Veall (1953) and Cox and Chalmers (1953) have studied the placental circulation using radioactive Na^{24}. They observed a diminished blood flow seen in this series. Is the placental ischaemia an aetiological cause in the toxaemic states? Perhaps the parallel of the vicious circle set up in hypertension and renal ischaemia can be more closely applied to the toxaemic states. In essential hypertension in the young adult it is a growing belief that in the overwhelming majority of cases a renal cause will be found if adequately investigated. This means aortography, preferably by individual catheterization of the renal arteries, which is quite practical when using the Seldinger apparatus. Perhaps more important than the arteries visualized is the intensity of the nephrogram phase, that is, while the contrast medium is in the arterioles and capillaries. This in turn is probably the best indication of renal ischaemia. It is the author's belief that if the criteria for nephrectomy in these cases were stricter, more "cures" would result.

If this concept is applied to the toxaemias it would perhaps explain why bed-rest alleviates the symptoms in some cases. In others, once the primary unknown cause of spasm has been established, the circle of spasm and ischaemia cannot be broken. Can the parallel be carried even further and the removal of the placenta be likened to a nephrectomy? Kaku (1953) presents the hypothesis that a polysaccharide in the placenta may start this circle by an antigen-antibody reaction.

Placental insufficiency would appear to fall into three groups:

(1) Spasm of the arteries in the toxaemic states preventing the blood reaching the placenta.

(2) Large retroplacental clots diminishing the effective function of the placenta.

(3) The third group appears to have no obvious physical cause but on examination of the delivered placenta it is seen to be unhealthy, friable and most of its surface thrombosed.

There is undoubtedly a fairly marked overlap between these groups with toxaemia of pregnancy playing a greater or lesser role in all three, and from the evidence at hand it appears to be important to assess the placental circulation in these cases in late pregnancy as a poorly circulating placenta may well be a deciding factor in the handling of a toxaemic patient.

There is, however, no doubt that placental insufficiency does occur *per se* with no relation to the toxaemic states or retroplacental clots.

Local Effects

In this series there has been no untoward effect on the punctured femoral artery. Occasionally small haematomata developed, but in all cases bleeding was controlled by firm digital pressure for a few minutes. There have been no cases of arterial thrombosis.

General Effects

With the use of Hypaque, and especially Urografin, it may be safely stated that we have had no unpleasant side-effects.

All cases on direct questioning will state that they get a feeling of warmth in the abdomen but in none was this painful. Only one case had nausea and she vomited 3 minutes after the injection. In this case the usual premedication had been omitted.

In no cases were there any ill effects to mother or foetus which could be ascribed to the examination. In no case did we induce labour in a patient not already in labour at the commencement of the examination.

Radiation and Comparison of Various Methods

Soft tissue placentography is firmly established. Excellent papers by Whitehead (1953), and numerous others have shown that the accuracy is high in such competent hands. More recently, Earn *et al.* (1958) have published a

paper claiming the exclusion of placenta praevia with one lateral radiograph to be absolutely reliable. Perhaps in less expert hands the error is greater. The author certainly has seen one case which showed the typical appearance of a placenta in the uterine fundus, and yet was a central placenta praevia. This film has been viewed by numerous radiologists.

Macafee (1956) stated that he discharged a case on the strength of a placentogram (using soft tissue methods) and a head engaged in the pelvis. The patient was readmitted a few days later with haemorrhage and required Caesarean section.

It is difficult to understand how soft tissue methods can demonstrate a placenta membranacea and, even if seen in the upper segment, its extension into the lower segment because of its unusual size may be considerable (Fig. 8).

The importance of this is obvious when one considers that soft tissue methods are not accurate in the diagnosis of placenta praevia. In the series of Earn *et al.* 12 out of 17 cases of placenta praevia were diagnosed correctly. This figure, 64 per cent, is a fair reflection of the accuracy of soft tissue methods in the hands of the average general radiologist, using only one film. If one takes all cases of ante-partum haemorrhage as a basis for analysis it is possible to be 90 per cent correct without taking a radiograph, as approximately 10 per cent of these patients will have placenta praevia. Surely then the degree of accuracy of any method of placental localization must be expressed as a percentage accuracy in the localization of the placenta praevia. This figure is stressed because, to discharge a patient with complete safety, one must accurately visualize the placenta, assess its type, position, size and circulation. Further, if there is a large concealed accidental haemorrhage present, or if placental circulation is poor, discharge of the patient is inadvisable. Only the arterial method can fulfil these criteria.

If due regard is given to radiation hazard then any method which reduces the exposure to mother and foetus must be given preference. The safety factor is then a balance of radiation against accuracy of localization. Whitehead's figures for accuracy are extremely high, but for a complete examination by his method the dose as measured at the centre of the foetus may obtain the order of 2·17 roentgens. Using the same method of calculating the dose, 90 per cent of this series received 0·37 roentgens, the remainder 0·74 roentgens.

Summary

The technique of arterial placentography by retrograde catheterization of the femoral artery has been described. Two hundred cases have been examined in 2½ years.

It has proved to be a safe and reliable examination for placental localization. It is useful for the assessment of placental insufficiency and concealed accidental haemorrhage. No other method of placentography can produce the same degree of accuracy in placental localization regardless of foetal presentation, duration of pregnancy, site of implantation and placental type.

It produces a graphic picture easily interpreted.

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I also wish to thank my colleagues in the X-ray Department, King Edward VIII Hospital, Durban, for their help and Dr. P. D. de Villiers in particular who was associated with the commencement of this series.

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A CONSIDERATION OF THE TREATMENT OF ELDERLY PRIMIGRAVIDAE

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WHILE obstetricians should, and do, regard all babies as precious, those of elderly primigravidae are especially so; not only is the mother's procreative life drawing to a close but pregnancy in such cases may be the crowning achievement of many years of infertile marriage.

The age at which a primigravida is considered "elderly" has never been generally agreed, and as Baird, Hytten and Thomson (1958) have shown, there is evidence of a decline of physiological efficiency from the age of twenty-five onwards.

Fredrikson and Anberg (1956) quote seventeen contributors among whom four concern themselves with the problems affecting the woman of thirty years and over, four with those of forty and over, and seven of the remaining nine choose thirty-five years as an arbitrary datum line (leaving two at thirty-six and thirty-eight years respectively).

In July, 1958, the Council of the International Federation of Gynaecologists and Obstetricians recommended that the age of thirty-five should be accepted as the international standard. In our survey we have adopted this criterion but in addition have further subdivided the group into those between the ages of thirty-five and thirty-nine inclusive, and those aged forty and over. Thus it is hoped to show differences with ageing, if such differences are significant.

There are many problems to be considered in the care and successful delivery of these patients. Questions as to the risk to the elderly primigravida from complications of pregnancy; the comparative safety or otherwise of the various methods of delivery; the frequency of stillbirth and neonatal death; the incidence of foetal abnormality; these and many others must be answered. It is therefore somewhat surprising to find that relatively little has been written on this subject during the last twenty-five years. Access to the records of large numbers of cases is an essential pre-requisite of any such investigation and this may account for the relatively few references in the literature. A noteworthy contribution has, however, been made by Waters and Wager (1950) from the Margaret Hague Maternity Hospital in Jersey City. This hospital has one of the largest delivery rates in the world and from this source they have analyzed the results in 649 cases, collected over a ten-year period. Arnot and Nelson (1950), Dennen and Ainslie (1951), Hawkins, Foley and Tierney (1951), Weisl (1953) and Fredrikson and Anberg (1956) are also worthy of mention.

In the Glasgow Royal Maternity Hospital we have encountered 662 elderly primigravidae during the eight years 1950 to 1957 inclusive. A group of primigravidae aged twenty-five and under who were delivered in the same hospital, was used as a control. In the first year of the survey 697 such primigravidae were delivered. A study of the Registrar-General's reports shows that primigravidae under twenty-five

encounter fewer maternal and foetal risks than any other group. Baird (1949, 1952) has commented on the factors which influence this. Such a method of control is open to the criticism that, while almost all elderly primigravidae have hospital confinements, a certain number of young and healthy primigravidae in Britain still have domiciliary confinements.

In the analysis of all the cases in the 1950–57 group, we considered all cases that were delivered in hospital irrespective of whether they were booked or emergency. This was done as it was felt that a truer picture can be appreciated of the overall problems associated with the treatment of elderly primigravidae. For the benefit of those readers who wish to know the foetal mortality in cases under the care of specialists in hospital—the ideal booked case—we have endeavoured whenever possible to show these figures separately. But this is only one aspect of a wider problem. That wider problem concerns the treatment of *all* elderly primigravidae whether booked or unbooked, in a city in which only 57 per cent of all confinements are conducted in hospital.

The hospital we write from is one which, by long tradition, has attracted a high incidence of abnormal confinements, and which serves a community engaged in heavy industry, in an area where housing and economic factors have long weighed heavily against the population. It is well known that contracted pelvis, severe anaemia and cardiac disease are still common in Glasgow. It is hoped therefore that the study of a sample from such a comprehensive source will serve to highlight the hazards to which the elderly primigravida is prone.

It was decided further to analyze the records of a similar group of elderly primigravidae who were delivered in the same hospital twenty-five years ago (1930–34 inclusive), prior to the introduction of chemotherapy and antibiotics. Comparison between the earlier and more recent groups will show to what extent the hazards to mother and child have lessened and will illustrate the changes in obstetric practice responsible for the improved situation. Perhaps the most striking contrast is seen in the comparison of maternal deaths, there being 11 in 244 (4·5 per cent) in the 1930–34 series, and only 1 in 662 (0·2 per cent) in the more recent one—the cause of death being post-anaesthetic cardiac failure associated with fatty degeneration of the myocardium. The 11 deaths in the 1930–34 series were due to sepsis (3 cases), haemorrhage (3 cases), chloroform poisoning (3 cases) and eclampsia (2 cases). Antibiotics, improved transfusion facilities, modern anaesthesia and better antenatal care have all operated in causing this dramatic fall in maternal mortality.

TABLE I

Perinatal Deaths—Combined Stillbirths and Neonatal (Hospital) Deaths, 1930–34 Compared with 1950–57

Group	Total	Perinatal Deaths	
		Number	Per cent
1930–34	258	71	27·5
1950–57	669	68	10·2
Booked cases only	368	29	7·9

The problem of maternal mortality would appear to have been solved during the last twenty-five years. In considering the child however, it will be observed that while there has been some improvement in foetal salvage, much yet requires to be done.

The perinatal death rate in the recent group is 10·2 per cent—just over one-third of that of twenty-five years ago (Table I). The high perinatal death rates reflect the state of affairs which can exist in a city hospital which deals largely with abnormal cases.

McKinley (1952), in a comprehensive study of the stillbirth rate in Scotland by age and social class of primiparous mothers, has shown the toll taken of infant life throughout the whole of Scotland (Fig. 1).

It would therefore appear that one of the many problems facing obstetricians today is that of lowering the perinatal death rate in elderly primigravidae. Various questions arise in this connexion. The complications of pregnancy and the various methods of delivery are linked up with the frequency and cause of stillbirth and neonatal death.

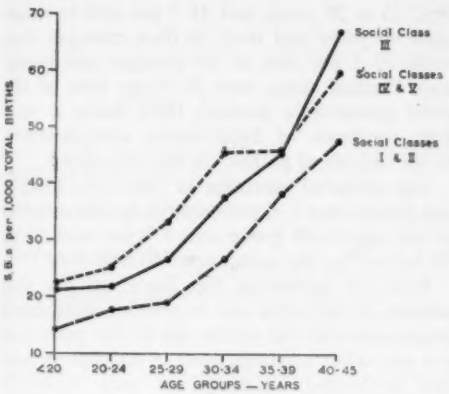

FIG. 1

Stillbirth rates in primiparae in Scotland by social class and age of mother (1951–55). (From data supplied by Dr. P. L. McKinley.)

FEATURES OF THE ANTENATAL PERIOD

In addition to the 662 patients delivered in hospital there were 40 cases of abortion before the 28th week. The incidence of abortion is difficult to assess in any circumstances. These figures do not suggest that the risk of abortion is outstanding in elderly primigravidae.

The antenatal complications most frequently encountered are shown in Table II. It will be observed that overall there is a much greater liability to complications in the elderly than in the young. In particular it will be noted that the elderly primigravida is more than twice as prone to hypertensive complications as the young primigravida. Nixon (1931) and Waters and Wager (1950), among others, made similar observations. The Glasgow cases show a higher incidence in both the sample and control groups than has been published elsewhere. The

TABLE II

Antenatal Complications

No.	Group	Hypertension		Pyelitis		Cardiac Disease		Anaemia		Fibroids		Others	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
697	Young primigravidae	110	15·8	19	2·7	16	2·3	19	2·7	—	—	12	1·7
662	Elderly primigravidae	214	32·3	8	1·2	16	2·4	47	7·1	31	4·7	28	4·2
363	Booked cases only ..	121	33·3	6	1·8	8	2·2	17	4·7	18	5·0	21	5·8

Percentage of complications in young primigravidae group=25·3
Percentage of complications in elderly primigravidae group=51·9

TABLE III

Hypertension Complicating Pregnancy

No.	Group	H.B.P. only (Mild P.E.T. and/or Essential Hypertension)		H.B.P.+Albuminuria (Severe P.E.T. and/or Eclampsia)	
		No.	Per cent	No.	Per cent
110	Young primigravidae ..	55	50	55	50
214	Elderly primigravidae ..	152	71·2	62	28·8
121	Booked cases only	100	82·6	21	17·4

high incidence of hypertensive complications must be particularly stressed as it inevitably finds its reflection in greater foetal hazard and loss.

Nelson (1955) has shown that the incidence of albuminuric pre-eclampsia is little affected by age but that the incidence of mild pre-eclampsia (hypertension without albuminuria) rises at the age of 30—corresponding with the time when the blood pressure begins to rise appreciably in the population as a whole. As Table III shows, our figures tend to support Nelson's work, there being a much higher incidence of hypertension alone in the elderly than in the young primigravidae.

While the high incidence of hypertension referred to above was anticipated, it was surprising to find the incidence of anaemia was also high. This was not due to unusual macrocytic anaemia but to the common microcytic iron-deficiency type, and could be the cumulative result of a greater number of years of poor dietary habit.

It is a popular assumption that fibroids are commonly encountered in pregnancy and labour among elderly primigravidae. Some support for this might be found where investigations have been concerned with small numbers of cases. Figures as high as 16·8 per cent (Randall and Taylor, 1949) have been recorded. Consequently it may have seemed reasonable in undergraduate teaching to stress the dangers of degeneration in pregnancy and obstruction in labour where this complication arises. In our series, however, the incidence of fibroids was only 4·7 per cent, and in many cases, as will be shown later, their presence caused no difficulty whatever. It is worthy of note that our figure is comparable with the incidence of 3·4 per cent quoted by Waters and Wager (1950) in their extensive survey.

In the breakdown of our series into those who were 35 to 39 years of age, and those who were aged 40 years and over, and considering all cases initially (i.e., booked and emergency) the most striking difference between these two groups was in the incidence of hypertension which emerged at 30·6 per cent and 45·5 per cent respectively. However when booked cases only were considered, the amount of hypertension was similar in the two age groups—33·2 per cent in those aged 35 to 39 years, and 31·2 per cent in those aged 40 years and over. It then emerged that while 55·6 per cent of the younger age group were booked cases, only 52·0 per cent of the older group were booked, there being a very high incidence of hypertensive complications in the unbooked patients in this age group.

The perinatal mortality in these two elderly age groups was 7·6 per cent (22 in 290 infants) in the age 35–39 group and 9·0 per cent (7 in 78 infants) in the group aged 40 and over.

Prior to surveying the literature on this subject, it had been our impression that more important than the actual age of the patient is the age of her marriage prior to conception and that prolonged infertility not only makes a delayed pregnancy more valuable but probably leads to obstetrical complications such as impaired uterine action. Daichman (1932) and Vara (1946) both subscribe to this point of view, suggesting that infertility (of 2 years duration or more) results in longer labours and more intervention. Most other authors (e.g., Nathanson, 1935; Fredrikson and Anberg, 1956) have found that infertility has no effect on the duration and type of labour in elderly primigravidae—or on the incidence of complications generally. Undoubtedly, because of the emotional factors involved, the amount and nature of intervention is not a good criterion by which to assess this factor. The series published by Arthur and Kaltreider (1956) included 93 patients who had been infertile for more than five years. Nineteen of these patients had inert labours, 17·2 per cent had Caesarean sections, and the perinatal loss was 6·4 per cent. The authors concluded that there was no real cause for concern in this infertile group of patients, the overall picture being the same in them as in all the elderly primigravidae in their series.

The duration of labour and mode of delivery of the 662 elderly primigravidae are shown in Tables IV and V. A large number of these cases (45·2 per cent) were unbooked. The tables therefore represent the practice not only of some fifteen obstetricians associated with the hospital, but also that of an unknown number of outside doctors and midwives who transferred patients to hospital in some instances where the outcome of the pregnancy was already prejudiced.

TABLE IV

Duration of Labour (Vaginal Deliveries)

Group		Total Number	Total Vaginal Deliveries	Less than 24 Hours		24–48 Hours		More than 48 Hours	
				No.	Per cent	No.	Per cent	No.	Per cent
Elderly primigravidae		662	503	341	67·8	114	22·7	48	9·5
Booked elderly primigravidae ..		362	280	190	67·9	69	24·6	21	7·5
Young primigravidae		697	686	498	72·6	149	21·7	39	5·7
Percentage perinatal loss in elderly primigravidae	All cases ..		13·7	11·7		15·8		22·9	
	Booked cases only ..		9·9	9·9		5·8		22·7	

In addition to the cases recorded in the table, 66 elderly primigravidae were delivered by Caesarean section during labour—36 after less than 24-hours labour, 18 after 24- to 48-hours labour, and 12 after more than 48-hours labour. Considering booked cases only, there were 36 sections in labour, 22 after less than 24-hours labour, 8 after 24- to 48-hours labour and 6 after more than 48-hours labour. There were only 7 Caesarean sections during labour in the young primigravidae—and indeed, because of the vastly different section rates in the elderly (23·2 per cent) and the young (1·6 per cent) primigravidae, these two groups are scarcely comparable in regard to length of labour prior to vaginal delivery.

Two-thirds of the elderly primigravidae were successfully delivered by the vaginal route within 24 hours. At first glance this would seem to be a highly satisfactory outcome. Indeed it is felt that these very figures, and others like them, may in themselves have engendered a feeling of optimism and occasionally complacency in the minds of obstetricians.

However, on closer examination of the associated stillbirth and neonatal death rates, the price paid in terms of foetal loss can be more accurately appreciated. Where the duration of labour before vaginal delivery is prolonged beyond 24 hours, the results are progressively less favourable. There are few who would be prepared to defend a policy of management of labour which entailed a duration greater than 48 hours, but in this series 9·5 per cent (48 cases) of those who had vaginal deliveries had been allowed to continue in labour for over 48 hours, and here the perinatal loss emerged at 22·9 per cent, a deplorably high figure.

TABLE V

Mode of Delivery

Group	Total No.		Spontaneous Vertex		Forceps		Caesarean Sections		Breech		Others	
	Infants	Mothers	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Elderly primigravidae ..	677	662	276	40·8	211	31·2	157	23·2	30	4·4	3	0·4
Booked cases only	368	363	154	41·9	116	31·5	84	22·8	14	3·8	–	—
Young primigravidae ..	702	697	566	80·5	80	11·4	11	1·6	37	5·3	8	1·2

TABLE VI

Perinatal Mortality (Combined Stillbirths and First Week Deaths)

Group	Total Number of Infants	Perinatal Deaths		Number Under 5 Pounds
		Number	Per cent	
Elderly primigravidae	677 (368)	68 (29)	10·0 (7·9)	39 (15)
Young primigravidae	702	32	4·6	20

Numbers in brackets=Booked cases only

The high perinatal loss is the kernel of the present-day problem in the management of elderly primigravidae (Table VI). Although there has been a great improvement during the past 25 years the foetal loss in this series gives no room for satisfaction.

An analysis of the perinatal loss related to mode of delivery makes interesting reading (Table VII). The more conservative the approach the higher the perinatal death rate. It seems an inescapable fact that, if we are to reduce our foetal loss we must introduce more radical methods.

The more frequent use of elective Caesarean section, as advocated notably by the Liverpool School, or, as has been already suggested by one of us (MacLennan, 1949), a more ready recourse to trial of induction of labour would, we suggest, materially improve the results. Indeed, between 1953 and 1957, Baird in Aberdeen has, by introducing a policy of early induction of labour, been able to show a perinatal mortality of 20 per thousand in elderly primigravidae (Baird, 1958). While it is not suggested that the samples are comparable, it will be readily agreed that the Aberdeen figures are approaching the irreducible minimum.

Relating the perinatal loss to mode of delivery, while helpful in pointing the above moral, would, if considered alone be of very limited value. This is borne out by examination of the associated clinical causes of perinatal death in the series which shows the commonest factors to be toxaemia of pregnancy and/or prematurity —43 (63·2 per cent) of 68 perinatal deaths were due to either of these causes, which are not necessarily affected by the mode of delivery. Twelve cases (17·6 per cent), however, were due to asphyxia in labour, a risk which can be affected by the mode of delivery, a risk to which elderly primigravidae are especially prone and one which has already been assessed by Turnbull and Baird (1957). A more radical approach would be justified in an attempt to reduce the

TABLE VII

Perinatal Loss Related to Mode of Delivery

Mode of Delivery	Group	Total	Perinatal Deaths	
			Number	Per cent
Spontaneous vertex ..	Elderly primigravidae ..	276 (154)	33 (14)	12·0 (9·1)
	Young primigravidae ..	566	17	3·0
Forceps	Elderly primigravidae ..	211 (116)	22 (9)	10·4 (7·8)
	Young primigravidae ..	80	5	6·3
Caesarean section ..	Elderly primigravidae ..	157 (84)	5 (1)	3·2 (1·2
	Young primigravidae ..	11	0	—

Numbers in brackets=Booked cases only

mortality due to toxaemia and intra-partum asphyxia. Non-toxaemic prematurity is a more complex problem, and its solution may have to await the abolition of some of Glasgow's unfortunate sociological problems.

The risk of foetal abnormality, including mongolism, which is incurred when the elderly woman embarks upon pregnancy, has often been the subject of comment. In our series the incidence of foetal abnormality was found to be 4·1 per cent in the elderly primipara, as compared with 1·9 per cent in the control group. Gross foetal abnormality—incompatible with life—was found in approximately the same proportions in both groups (66·7 per cent and 69·2 per cent respectively, of the abnormal babies encountered). Although it is apparent that 1 in 25 elderly primigravid mothers will thus have a congenitally abnormal baby, and that this risk is more than twice that in the young primigravida, the joy of a healthy though "late" baby to a comparatively aged mother must—and indeed does—far outweigh this risk.

Fibroids, as has been mentioned earlier, were encountered in 31 (4·7 per cent) of the 662 patients in this series. There were none in the 697 young primigravidae of the control group. Of the 31 cases, only 8 had complications which might be attributed to the associated fibroids. Retained placenta requiring manual removal occurred in 4 patients, one of whom had a threatened miscarriage earlier in the pregnancy. The other 4 patients had a prolonged labour due to uterine inertia, a Caesarean section being performed after more than 48 hours of labour.

Fourteen of the remaining 23 cases were delivered by Caesarean section for other reasons —hypertension, 6 cases; contracted pelvis, 3 cases; and in 5 cases elective section was performed simply because of the patient's age and the associated fibroids.

Summary

An eight-year series (1950–57 inclusive) of the elderly primigravidae delivered at the Glasgow Royal Maternity and Women's Hospital has been analyzed and compared with a similar five-year series at the same hospital 25 years ago, and also with a control group of primigravidae aged 25 years and under.

The maternal and perinatal mortality, antenatal complications, the mode of delivery, the duration of labour, and finally the incidence of foetal abnormality and uterine fibroids were all considered.

Conclusions

(1) In the elderly primigravidae the maternal mortality is no longer a problem.

(2) The high perinatal loss in this series suggests that all elderly primigravidae should be admitted to hospital for assessment before term.

(3) A more radical approach to the actual hospital confinement and trial of induction or elective Caesarean section can be justified by the improved perinatal foetal results which accrue.

(4) The high incidence of toxaemia of pregnancy still presents a major problem in these cases.

Acknowledgments

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SOLID OVARIAN TERATOMA WITH STRUMA OVARII, THECA LUTEIN REACTION, AND ENDOMETRIAL HYPERPLASIA

Report of a Case

BY

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IN recent years a body of case reports and small series has emphasized the observation that ovarian tumours which are usually considered to be endocrinologically inert can, on occasion, be associated with the clinical symptoms and anatomical stigmata of endocrine activity. Morris and Scully (1958) have summarized the relevant literature under the general title of tumours with "functioning stroma", citing examples from their experience and from the literature in which cystadenomas, carcinomas, Brenner tumours, and Krukenberg tumours have been associated with signs of oestrinism or, rarely, of virilism. Many cases have been associated with one or another of the forms of endometrial hyperplasia. The common morphological denominator is the presence in the stroma of the tumour of "clusters of diffuse zones of polyhedral or rounded, fat-containing cells similar in appearance to luteinized theca or stromal cells". Hughesdon (1958) has recently studied 10 cases of ovarian carcinoma in which such a thecal reaction was observed; in 6 cases the endometrium was available for study; 4 instances of cystic hyperplasia were noted; in 1 case the uterus was removed a month after the ovarian tumour; in another case the endometrium was described as "atypical proliferative". The occurrence of this thecal reaction in association with a teratoid tumour of the ovary has not yet been described.

Struma ovarii (Smith, 1946) is a teratoid tumour of the ovary in which the thyroid element is prominent, dominant, or even the only element present. Thyrotoxicosis and hyperplasia of the thyroid element has been reported in a few cases (Gusberg and Danforth, 1944) and malignant change very rarely (Rotton and Tovell, 1956). There is no reliable information regarding its association with endometrial hyperplasia.

CASE REPORT

A 64-year-old white woman complained of post-menopausal bleeding of 2-years duration. Menarche occurred at 12 years and menstruation had been somewhat irregular, but she had had 10 essentially normal deliveries. Menopause had occurred at age 45. There was no vaginal bleeding for 17 years. For the 2 years before admission she had observed almost monthly vaginal bleeding lasting 4–5 days accompanied by a yellowish discharge. Abdomino-pelvic examination revealed the uterus to be irregular, enlarged to the size of an 8-weeks gestation. A hard mass was felt in the right adnexal area. The cervix was firm and closed. The uterus and right adnexal mass were freely movable. Signs and symptoms of hypertensive cardiovascular disease were present. The remainder of her clinical, roentgenographic, and laboratory investigations were unrevealing and unrelated to her gynaecological disorder. Dilatation and curettage were performed. Eight days later a total abdominal hysterectomy, bilateral salpingo-oöphorectomy, and appendectomy were performed.

Pathological Observations

The uterus measured 11 cm. long by 8 cm. in transverse diameter, and contained several leiomyomas in its wall. The endometrial cavity was lined by a granular, roughened, and partly eroded mucosa from which several small, soft polypoid tags protruded into the cavity. The cervix was not unusual. The Fallopian tubes were normal in appearance. The left ovary measured 2·7×1·5×1·0 cm., showing a yellow-tan, somewhat gyriform surface. On section the cortex was 3 mm. thick, and tan. The right ovary was almost spherical, measuring 2·5×2·2×2·1 cm. A number of thin-walled cystic spaces up to 5 mm. in diameter were seen beneath the surface. The central portion was occupied by a spherical tumour mass 1·8 cm. in diameter. The mass was soft, bulged on section, and was variegated in colour, ranging from pale tan to light yellow-green with interspersed pinkish zones. It was not definitely encapsulated but was separated from the cortex by a thin, irregularly folded layer of bright yellow tissue. Several cavities were seen in the substance of the tumour, but for the most part it was solid, tan, and slightly translucent.

Microscopic examination of the tumour in the centre of the right ovary revealed it to be a complex solid adult teratoma composed of about 90 per cent mature thyroid tissue, the remainder comprising adipose tissue, sweat glands, an occasional nodule of hyaline cartilage, and a few cystic spaces lined by a ciliated, respiratory type of epithelium. The thyroid tissue was in the form of small acini lined by cuboidal epithelium. For the most part they contained little or no colloid; however, a few acini were distended by large accumulations of colloid and lined by flat epithelium, and a few showed marginal vacuolation of colloid. There was no evidence of papillary infolding, lack of uniformity, hyperplasia, or neoplasia.

The teratoma was situated in the medulla of the ovary. Separating it from the cortex and from the structures at the hilus was a discontinuous rim, variable in thickness, of polyhedral cells (Fig. 1). These cells were clearly derived from the substance of the ovary and were not part of the teratoma, but peripheral to it. They were continuous with the cortical stroma, in contact with tongues of cortical stroma which penetrated the medulla, and blended into the connective tissue framework of the hilus, and in no sense were they intrinsic to the teratoma. Topography, therefore, furnished no clue as to the origin of the polyhedral cells. The more frequent form of the polyhedral cells consisted of a relatively small cell with a homogeneous, densely eosinophilic cytoplasm and a dark, unstructured, centrally placed nucleus (Fig. 2). They were arranged in small clusters or aggregated with no distinctive growth pattern, and merged by degrees into a slighly less numerous, though rather conspicuous form, a cell characterized by an abundant, clear, finely vacuolated cytoplasm, sharply defined cell interfaces, and an equally nondescript nucleus (Fig. 3). The small oxyphilic cells resembled the theca-lutein cells normally seen at the periphery of a normal corpus luteum, but could not be definitely distinguished from proliferations of hilar cells. However, because of the apparent transition from spindle-shaped stromal cells into these polyhedral oxyphilic cells (Fig. 4) as well as because of the absence of crystalloids of Reinke, lipochrome pigment, or association with nerve fibres, I interpret them as theca-lutein cells. If this is valid, the large, clear cells presumably are luteinized theca in the phase of storage of metabolized substances, presumably lipids. A silver impregnation for reticulum showed delicate argyrophilic reticulum coursing between the individual cells comprising this zone of luteinized theca, supporting the notion of its stromal origin. Sections stained with periodic acid (Schiff-McManus) showed no PAS-positive material in the theca-lutein cells, although the colloid in the thyroid follicles of the teratoma was positive.

Material was not available for lipid stains to demonstrate sudanophilic material. The overlying ovarian cortex was densely cellular and somewhat compressed showing strong basophilia. No areas of stromal loosening were seen surrounding the zone of thecal reaction. A rather prominent rete ovarii was present in the hilus, but no hilar cells were evident in the vicinity.

Sections of the left ovary showed a somewhat thickened cortex with densely packed stromal

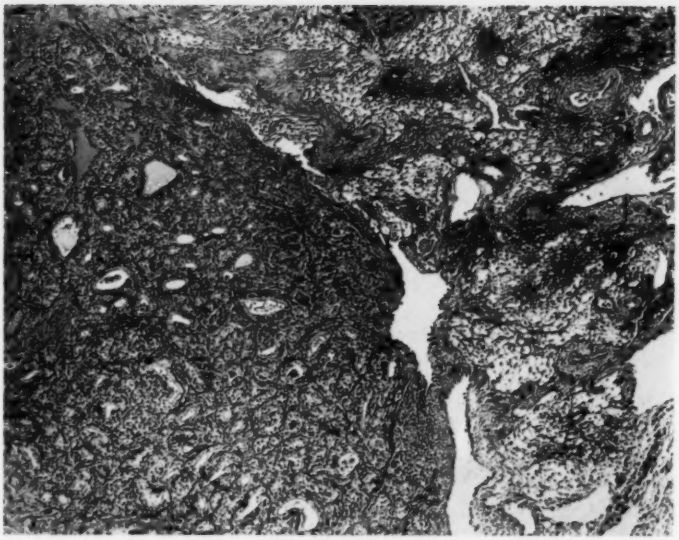

FIG. 1

Low power view showing the relationship of the struma ovarii to the surrounding zone of luteinized theca. ×30.

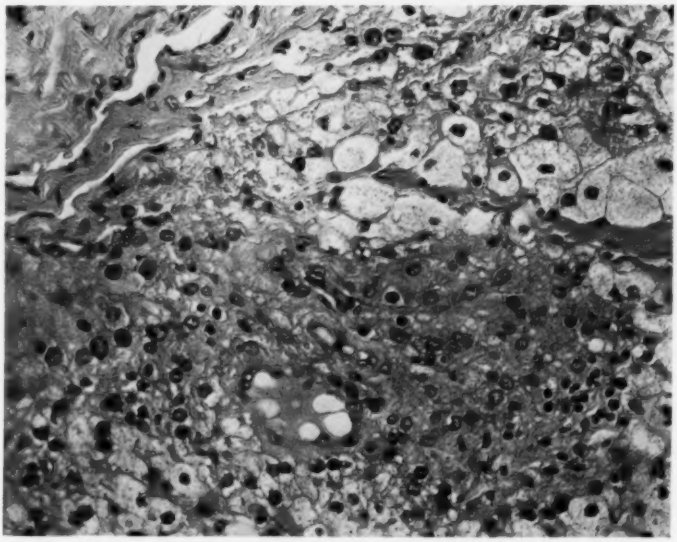

FIG. 2

Detail of the luteinized theca showing small polyhedral oxyphilic cells with transitions to clear cell forms. ×225.

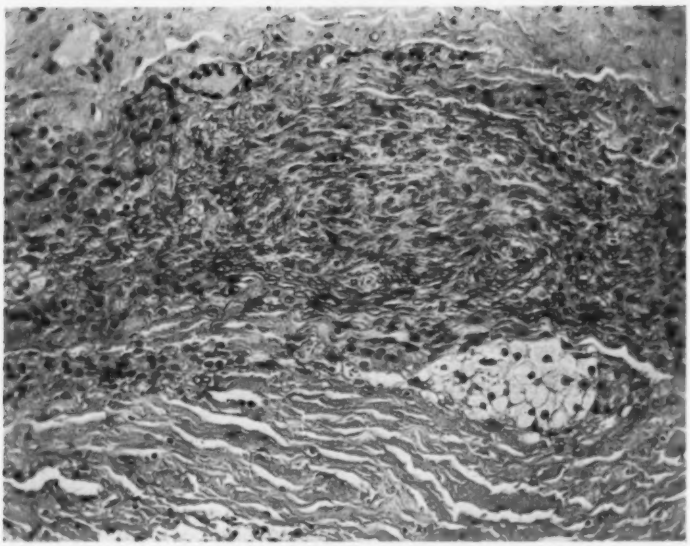

FIG. 3

A tongue of spindle-shaped stromal cells showing apparent transition to polyhedral oxyphilic cells at the left and to both oxyphilic cells and clear cells at the lower border. ×75.

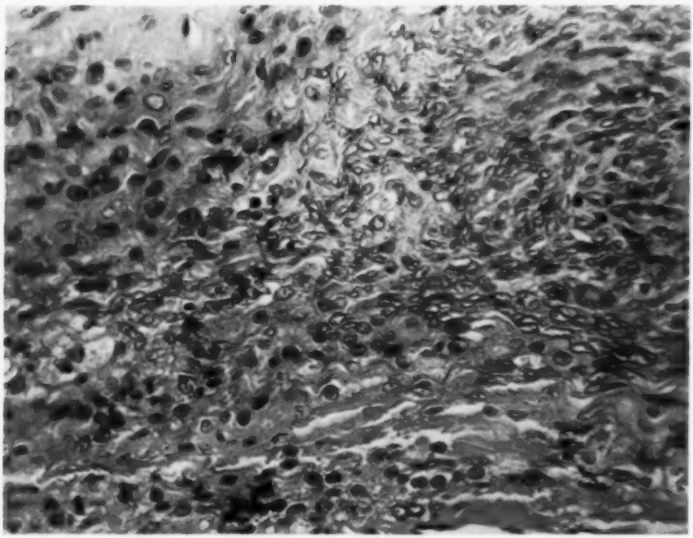

FIG. 4

Detail of the left hand margin of Fig. 3 showing the zone of transition. At the left margin a few plumper cells with clearer cytoplasm are seen abutting on the smaller oxyphilic cells. ×225.

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FIG. 5

Low power view of the endomyometrium showing a sessile polypoid growth pattern with a few cystically dilated glands. ×15.

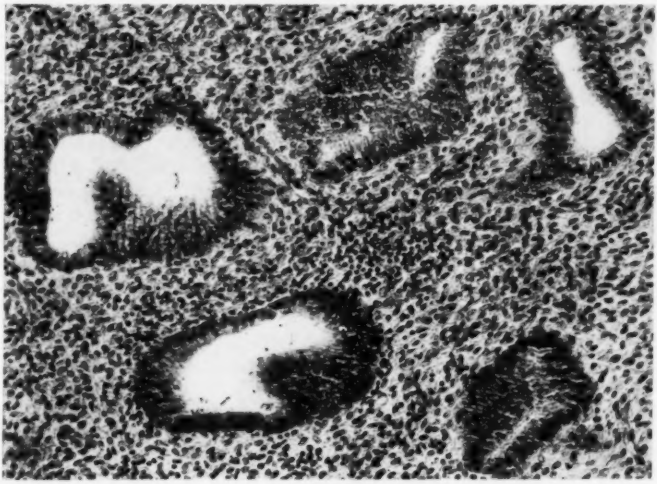

FIG. 6

Detail of the endometrium showing glands with irregular contours, nuclear crowding, accentuated stratification, and a cellular stroma with sparse lymphocytic component. ×90.

cells. These extended as dense, basophilic aggregates deeply into the medulla between ancient corpora albicantia. There were no luteinized theca cells. Again, a prominent rete ovarii was present but hilar cells were absent.

The endometrium as seen both in curettings and in the removed uterus showed a moderate degree of polypoid and cystic glandular hyperplasia. The polypi were small and sessile (Fig. 5); they did not show well-developed stromal or vascular cores. The hyperplasia was principally of the glandular epithelium. The glands were tortuous and showed moderate stratification of columnar cells (Fig. 6). A few glands were cystically dilated. Occasional mitoses were seen in the glandular epithelium, but they were by no means frequent. The endometrial stroma showed a variable density to its cellularity, some areas being loose and slightly oedematous, other areas being more closely packed. Stromal mitoses were not observed. The stratified squamous epithelium of the exocervix was well cornified and well glycogenated.

Discussion

From the foregoing observations, one assertion can be made without reservation, namely, that a theca-lutein reaction can occur sporadically in association with a teratoid tumour as well as with a non-teratoid tumour. It is a plausible inference that the endometrial hyperplasia represents a response to hormones, presumably oestrogenic, elaborated by the luteinized theca cells. In this case there was no evidence of the loosening of ovarian stroma that is sometimes found in similar situations; Hughesdon (1958) has described it well, but the phenomenon is inconstant. There was neither clinical nor pathological evidence of overactivity of the thyroid element in the teratoma. This case is not comparable to the one described by Murray *et al.* (1942) in which there was struma ovarii in one ovary, a granulosa cell tumour in the other ovary, and hyperplasia of the endometrium presumably secondary to the granulosa cell tumour.

There are several possible theories which might be conjured up to explain the development of the occasional theca-lutein reaction in the stroma of ovarian tumours: (1) The luteinization is the effect of increased pituitary gonadotrophin in the post-menopausal period. This mechanism does not explain instances occurring in pre-menopausal women, nor does it take into account the rarity with which the theca-lutein reaction is seen in contrast to the frequency of post-menopausal increase in gonadotrophin. Also, in post-menopausal women it is FSH which is elevated rather than LH; the latter is probably not secreted. However, in pre-menopausal women elevations of LH are often associated with hyperthecosis and thecal luteinization. If an hypophyseal stimulus is necessary for the condition, appropriate alteration in the sensitivity of the end organ to this would be equally necessary. (2) The luteinization is the effect of a stimulus from the adrenal cortex. Stromal luteinization has been observed on occasion in the ovary associated with certain cases of adreno-cortical hyperplasia, the adrenogenital syndrome, and in Cushing's syndrome, albeit inconstantly. Whether this is referable to stimulation by a corticoid or by excess pituitary gonadotrophin elaborated secondary to the primary adrenal lesion is not known. It seems a singularly roundabout mechanism to explain the phenomena seen in this case. (3) The theca-lutein reaction is not due to endocrine stimuli outside the ovary but is mediated entirely by local, intra-ovarian mechanisms. Precisely what these mechanisms might be is a matter of speculation. Follicle ripening with thecal luteinization is often seen in the ovaries of pre-pubertal girls independent of any rise in gonadotrophin titre, albeit low "background" levels of FSH may be present. (4) The unilateral occurrence of the theca-lutein reaction in this case is probably the major substantive evidence that it is a local response to the presence of the tumour rather than the result of a hormonal stimulus from outside the ovary.

The absence of any evidence to permit selection among these alternatives (or even hypotheses regarding additional explanations) reflects the observation that the theca-lutein reaction of the stroma in and around ovarian tumours is infrequent and not clinically predictable. It is usually discovered by microscopic observation after surgical removal of the tumour has been

completed, thereby vitiating attempts at comparing pre-operative with post-operative levels of appropriate hormones. In two cases of Krukenberg tumour (Turunen, 1955) in which a theca-lutein reaction and endometrial hyperplasia were present, there was a fall from elevated pre-operative oestrogens levels to normal.

It is evident from the foregoing that "luteinization" is a term which has been used loosely to describe alterations in the mesenchymal cells of the ovary (granulosa, theca interna, theca externa, cortical stroma). While undoubtedly, biosynthesis of steroid hormones is the common denominator of luteinization, the variations in this process make for significant clinical differences. There is no guarantee that the same chemical change is involved in all situations. Can we say that a luteinized granulosa cell in a normal corpus luteum elaborates the same steroids as a luteinized theca cell in the same corpus? Or that stromal luteinization is identical with thecal luteinization in respect to cause, function, or clinical implication? There is substantive evidence that theca cells elaborate both oestrogens and androgens. Inert steroid intermediates are also present. There is little evidence which bears upon the circumstances under which the amounts, proportions, synchronization, and specific compounds are elaborated and liberated. It is clear that more precise chemical classification of the lutein response is necessary. We must avoid oversimplification of the homeostatic stimulus-response schema. Luteinization which may be "physiological" in one context may be exaggerated and inappropriate in another.

Summary

(1) Post-menopausal bleeding led to the discovery of a unilateral ovarian tumour, which on examination proved to be solid adult teratoma composed largely of thyroid tissue. It was surrounded by a zone of polyhedral cells identified as luteinized theca cells. Endometrial hyperplasia was present. The contralateral ovary showed no luteinization.

(2) A mild degree of oestrogenic activity is ascribed to the theca-lutein reaction in this case. A variety of possible mechanisms for its development are outlined. It is felt that the reaction is a local response to the presence of tumour. The incompleteness of our current knowledge of the cause and effect of luteinization is acknowledged.

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SECONDARY ABDOMINAL PREGNANCY

BY

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SECONDARY abdominal pregnancy presents a fascinating problem and is of special importance in countries where ruptured ectopic gestation tends to be neglected.

A good number of such interesting cases have been published in the past. Chassar Moir (1956) discusses all features of the subject, quoting from the literature, particularly from Mahfouz (1938), Charlewood and Culiner (1955) and King (1954). De Villiers (1954) reviewed the literature of abdominal pregnancies at or near term for the previous 10 years. Podday (1957) has recently reviewed the world literature. Table I summarizes the number of cases collected by recent authors. The average maternal mortality of all these collections is 10·2 per cent (209 cases).

Certain developments tend to arise from a persisting abdominal pregnancy:

(1) Recurrent abdominal pain and discomfort due to

(*a*) recurring haemorrhage in connexion with the gravid sac;

(*b*) gastro-intestinal disturbances from pressure and displacement by the enlarging sac;

(*c*) infection.

(2) Early foetal death, spurious labour or postmaturity with loss of foetal movements.

(3) Foetal deformities, due to pressure from oligohydramnios and amniotic bands.

Thus it is now well accepted that laparotomy should be undertaken as soon as the diagnosis is

TABLE I

Comparison of Cases Reported in Recent Literature

Author	Date	No. of Cases	After 28-Weeks Maturity	Viable Infants Born Alive	Placenta Removed	Death Related to Placental Removal	Maternal Mortality Per Cent
de Villiers (Collected) ..	1954	77	77	47	39	1	5·2
King (China)	1954	12	12	1	9	nil	nil
Charlewood and Culiner (South Africa)	1955	52	52	12	24	7	13·4
Sison and Aragon (Philippines)	1956	24	18	5	?	3	18·18
Hibbard (Los Angeles) ..	1957	23	5	1	15	nil	4·3
Zuspan *et al.* (Ohio) ..	1957	11	5	1	2 of 5	nil	nil
Podday (India)	1957	10	2	nil	9	1	30·0
Total		209	171	67	98	12	10·2
Present series (Ibadan) ..	1959	9	5	1	5	nil	nil

TABLE II
Details of Gestation Features in the Ibadan Cases

Case No.	Age	Parity	Period of Gestation	Maturity of Foetus	Type of Extra-uterine Pregnancy	Foetus at Birth
1	26	5	36 weeks	36 weeks	Twins, one intra-uterine, one extra-uterine	Both stillborn
2	28	1	18 weeks	18 weeks	Abdominal	Fresh
3	30	6	2 years	18 weeks	L. tubo-abdominal	Macerated
4	32	5	44 weeks	Postmature	Infected abdominal	Mummified
5	20	0	9 months	30 weeks	L. unruptured tubal	Macerated
6	35	4	20 weeks	20 weeks	Abdominal	Alive
7	25	0	26 weeks	26 weeks	Abdominal	Alive
8	28	2	44 weeks	Postmature	Abdominal, hydramnios	Macerated
9	33	1	36 weeks	36 weeks	R. tubo-abdominal	Alive, survived

made. Chassar Moir points out the dangers of delay. He says it is questionable whether even in exceptional circumstances a short delay is justifiable in order to obtain a live baby unless the patient is under close supervision and the baby appears normal.

The earlier in pregnancy the operation is performed the less risk is there of severe haemorrhage from the placental site during the operation and thus the greater likelihood that removal of the placenta, which is the ideal treatment, is possible.

At University College Hospital, Ibadan, 9 cases of secondary abdominal pregnancy have been collected during the 3-year period 1st October, 1955, to 30th September, 1958. Of these, 7 were fully diagnosed before operation and in 5 cases the foetus had reached a viable maturity. One baby of 36 weeks survived. The foetus was alive at operation in 2 of the patients whose pregnancy was under 28 weeks mature. There were no maternal deaths.

Because of the importance of making an early diagnosis, these 9 cases are analyzed to show the features which lead to early discovery. A summary of certain features is made in Table II. The cases are tabulated in order of occurrence.

DIAGNOSIS

The diagnosis depends on:

History

(*a*) symptoms of threatened or early rupture (4 of 9 cases).

(*b*) persistently recurring abdominal pain—a prominent symptom in the later months of pregnancy (7 of 9 cases, see Table III). This is the most important single factor to be obtained from the history.

(*c*) cessation of foetal movements, spurious labour and postmaturity.

Physical Signs

The classical features on abdominal palpation are not always easy to elicit especially in an early case. However, abdominal tenderness and abnormally high-lying foetal parts are usually present, frequently associated with a persistent malpresentation. A cystic swelling in the abdomen may be thought to be ovarian and then prove to contain foetal parts.

Vaginal examination is of great value. The cervix may be long and firm like a "non-pregnant" cervix, as occurred in 4 cases in this series; it may also be displaced upwards and forwards. The uterus may be felt separate from the mass or mistaken for a fibroid.

X-ray Examination

Radiographic findings are of the greatest assistance in the diagnosis and presented classical features in 7 of the 8 cases X-rayed. The detailed findings have been described by de Villiers (1954) and Todes (1958). The main diagnostic features are:

(*a*) an abnormally high position of the foetus above the pelvic brim, usually associated with malpresentation (Fig. 1);

FIG. 1a
(Postero-anterior view)

FIG. 1b
(Lateral view)

The hyperextended foetus is lying high above the pelvic brim. The skull is collapsed. Within the sac are seen gas bubbles of varying sizes. The investing soft tissue shadow is 3·5 cm. thick (Case 4).

FIG. 2

X-ray of foetus of 28-weeks maturity taken shortly after delivery alive, showing pressure deformities and acute flexion of spine (Case 7).

FIG. 3

Hysterogram showing the slightly enlarged uterus displaced to the left. The foetus of 34 weeks is lying transversely high above the pelvis (Case 9).

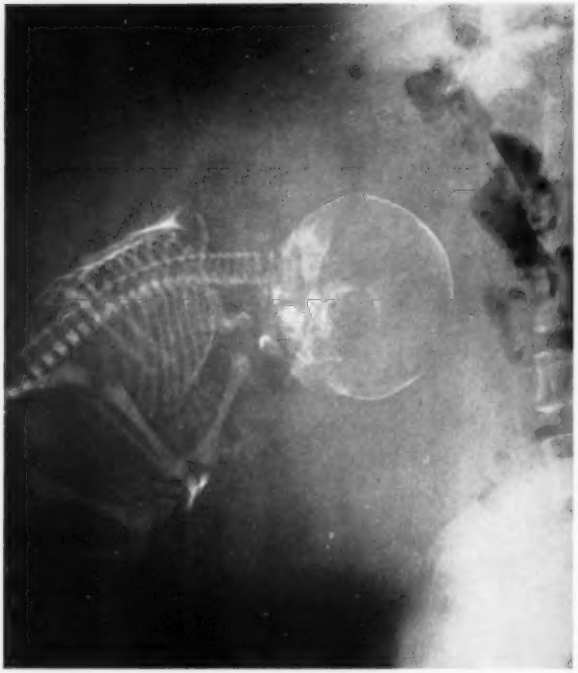

FIG. 4

Lateral X-ray of abdomen showing single foetus, near term, lying obliquely with marked hydramnios and a pendulous abdomen (Case 8).

TABLE III

Summary of the Clinical History and Features at Operation

Case No.	History of Tubal Rupture	Immediate Presenting Symptoms	Initial Diagnosis	Features at operation	Placenta Removed
1	No	Retained second twin	Retained twin, probable ruptured uterus	Extra-uterine twin	Yes
2	Yes	Severe anaemia, abdominal pain	Extra-uterine pregnancy	Haemoperitoneum	Yes
3	No	Abdominal pain and distension	Abdominal abscess	Infected old abdominal pregnancy	Yes
4	No	Abdominal pain, fever, pregnancy overdue	Infected abdominal pregnancy	Infected abdominal pregnancy	No
5	No	Foetal movements ceased, vaginal bleeding	Intra-uterine death	Macerated foetus, dilated tube	Yes
6	Yes	Abdominal swelling, pain following "abortion"	Ovarian cyst	Amniotic band deformities	No
7	Yes	Abdominal pain, weakness	Extra-uterine pregnancy	Foetal pressure deformities	Yes
8	No	Abdominal distension, pregnancy overdue	Hydramnios, pre-eclampsia	Abdominal pregnancy with hydramnios	No
9	Yes	Vomiting, abdominal pain	Extra-uterine pregnancy	Recent peritoneal bleeding, pressure deformities (temporary)	No

(*b*) distortion of the foetus with extension or acute flexion of the foetal spine and bizarre-shaped head. These abnormalities do not necessarily indicate foetal death; they may be due to pressure and oligohydramnios (Fig. 2);

(*c*) absence of the uterine shadow surrounding the foetus.

In order to avoid an incorrect conclusion, it must be noted that the soft tissue wall covering the foetus is not invariably thinner than the uterine wall, as suggested by King (1954), but in the presence of infection may be as much as 3·5 cm. thick (Fig. 1).

Other features seen on X-ray have been described. The non-pregnant uterus may cast a separate shadow. Gas may be seen in the maternal ileum abnormally near the foetal head or intestinal shadows seen intermingling with foetal parts. In one infected postmature abdominal pregnancy gas was present inside the sac and actual crepitations were palpated beneath the abdominal wall (Case 4).

Additional Investigations

Hysterogram investigation has been reported but has only been used in cases where foetal death was evident. In Case 9 of this series the foetus was alive and mature; hysterogram gave final proof to the diagnosis (Fig. 3). In such a case preparation should be made for laparotomy

on the same day, in order to avoid unnecessary foetal death should spurious labour ensue following the investigation.

Tocographic tracing may be helpful, in advanced cases, to show absence of the normal Braxton Hicks uterine contractions. It was found useful in Case 7. Pitocin drip may be used to demonstrate absence of the normal uterine response, though the results are not very reliable.

Two cases in this series, 1 and 3, were not fully diagnosed before operation. It is unusual to diagnose a combined intra- and extra-uterine pregnancy before delivery of one twin. Winer *et al.* (1957) in a survey of 68 cases found only 7 with a tentative diagnosis made beforehand.

Another patient had gross hydramnios associated with the abdominal pregnancy. Only one other example of this association could be traced in the literature. King described a patient in whom the foetus was alive; spontaneous rupture of the amniotic sac caused acute abdominal symptoms and at operation the peritoneal cavity was found to be flooded with amniotic fluid. Actually oligohydramnios is usually present causing pressure deformities. This deficiency of liquor amnii may be due to lack of the transudation factor owing to the poor maternal blood supply to the amnion, in the absence of the normal vascular uterine layer surrounding it. If this be so, the gross hydramnios in Case 8, detailed below because of its rarity, is difficult to account for.

Case 8

On admission after 10-months amenorrhoea, this patient stated her abdomen had increased in size with some abdominal pain for the past month. She was mildly febrile with a moderate pre-eclampsia; the abdominal girth was 102·5 cm. (41 inches); no foetal parts or foetal heart were detected owing to the tense hydramnios. The haemoglobin was 50 per cent. X-ray examination confirmed hydramnios with a single foetus present, lying transversely, showing no evidence of foetal death or abnormality (Fig. 4). Abdominal paracentesis of 900 ml. produced slightly brownish liquor amnii.

It was not until the cervix was examined with a view to induction of labour and noted to be unusually long and firm, that any further abnormality was suspected. The separate uterus was then felt anterior to the hydramnios.

After a blood transfusion, examination under anaesthesia was performed followed by abdominal section. A macerated foetus of 4 pounds 8 ounces was delivered together with floods of liquor amnii. The placenta was not removed since it was attached to the lateral pelvic wall as well as to the uterus. The sac was thick-walled and the cavity so large that it was thought best to drain it. Post-mortem examination of the foetus revealed no abnormality.

There was a swinging pyrexia post-operatively for 6 weeks in spite of chemotherapy and blood transfusion. After 7 weeks the necrotic placenta was removed at a further operation.

Treatment

It is undoubtedly best for the patient if the placenta and sac can be safely removed together with the foetus at the time of laparotomy. Recovery was considerably shortened in the 5 cases in this series in which this was possible. However, the highest mortality in the literature (see Table I) is still due to haemorrhage on separation of the placenta. There is usually less bleeding associated with its removal when the foetus has been dead for some time, but Charlewood and Culiner (1955) reported 4 exceptions and to attempt delaying operation on this account is not justifiable.

No drainage of the sac is necessary whether or not the placenta is retained, except in frankly infected cases. It is important to avoid disturbance of the sac as far as possible in the presence of infection. The infected sac in Case 5 had perforated into the rectum; at operation the placenta and sac were left untouched and a wide-bore drain inserted. Of two similar cases found in the literature (Masterton and Baum, 1956; Hibbard, 1957), there was partial removal of sac and placenta which may have been a considerable factor in their fatal outcome.

Close watch should be kept on the patient whose placenta is retained in the abdomen without drainage, since the sac may become infected as late as 7 weeks after the operation. This occurred in Case 9; on abdominal section a live baby of 4 pounds 1 ounce was delivered, the placenta was thick and friable, adherent to lateral pelvic wall and removal at the time would undoubtedly have been disastrous. The abdomen was closed without drainage. There was very little fever post-operatively, some fluid which had formed in the sac after 2 weeks was aspirated, but after 7 weeks the sac suddenly became infected requiring a second laparotomy; this time the placenta, still weighing 1 pound 3 ounces, was easily shelled out.

Summary

Nine cases of secondary abdominal pregnancy were operated upon at University College Hospital, Ibadan, during the 3-year period ending September, 1958. These cases are analyzed.

In 5 cases the foetus was of viable maturity, one was alive and survived. There were no maternal deaths.

The earlier diagnosis of abdominal pregnancy is advocated. Seven of these 9 cases were diagnosed before operation. Careful X-ray interpretation provides the most important aid to diagnosis in conjunction with the history and physical signs.

Foetal deformities were due to oligohydramnios and amniotic bands. One case complicated by gross hydramnios is described in detail.

Special points in the treatment are outlined.

Acknowledgments

I wish to thank Dr. J. B. Lawson, Head of the Department, and Dr. U. G. Lister, Senior Lecturer, for permission to include the cases which were under their care. I am also indebted to Dr. W. P. Cockshott, Department of Radiology, for his help and interest in the radiographic interpretation.

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A CASE OF OBSTETRICAL ACUTE YELLOW ATROPHY OF THE LIVER

BY

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OBSTETRICAL acute yellow atrophy of the liver as distinct from true acute yellow atrophy and delayed chloroform poisoning was first described by Sheehan in 1940. By virtue of its rarity, it is difficult to give its incidence; throughout the literature there is little mention of the disease, but Moore (1956) reviews the literature and accepts 13 cases (on the basis of the histological picture of the liver) since 1934 and adds 4 cases of his own.

Sheehan's summary of the clinical findings is as follows:

> "At 36–40 weeks there was a sudden onset of vomiting and spasmodic pain followed in a few days by jaundice. These symptoms progressed very rapidly, the jaundice became very intense, the vomit was of coffee-grounds in appearance, and headache was sometimes present. After 7–12 days, the patient was delivered of a stillborn foetus, became comatose and died three days after delivery."

The lesion within the liver is that of a massive fatty infiltration, particularly marked in the central area of the lobule. In the case described below, it is unfortunate that liver biopsy was omitted, but the patient's condition made this investigation undesirable.

CASE REPORT

The case described is that of a primigravida, aged 22 years, whose L.M.P. was on the 23rd June, 1958, and whose E.D.D. was the 30th March, 1959. She had always been a healthy person with regular menstruation, except that for some years she had suffered from severe dysmenorrhoea. Earlier in this pregnancy miscarriage had threatened, but this was successfully overcome.

Her antenatal care was undertaken at a local maternity hospital, and there on the 5th March, 1959, she was admitted because of a high blood pressure (160/105) and persistent ankle oedema, neither of which had responded to treatment. On examination she was near term with the vertex presenting in the L.O.A. position and still above the brim.

On a regimen for pre-eclamptic toxaemia she rapidly improved. However, on the 15th March, 1959, she started to vomit and this increased both in amount and frequency over the next 4 days and she also complained of vague abdominal pain.

On the 19th March, 1959, her blood pressure had risen to 150/105; she had only passed 1 ounce of urine in 24 hours. She was slightly icteric with purpuric spots on the skin and bleeding gums. Examination of the urine showed the presence of albumin and acetone. At this stage she was transferred to our care.

On admission her general condition was very poor, the skin and tongue were dry and the gums were bleeding slightly. A few purpuric spots were seen on the skin, but Hess's test was negative. She was slightly icteric; the blood pressure was 150/70 and there was slight nystagmus and the reflexes were brisk. Her temperature was normal. On abdominal examination, the uterus was at term and the vertex well down and the foetal heart audible and regular in rate. The liver was not enlarged or tender and the spleen was not palpable. Pelvic examination showed that there was no disproportion and that the cervix was soft and well taken up. Throughout the examination there was copious vomiting.

Treatment

Initially, blood was taken for biochemical analysis and a catheter specimen of urine for routine investigation. They were reported on as follows:

Blood Biochemistry

Blood urea 55 mg. per cent; sodium 265 mg. per cent; potassium 16·5 mg. per cent; chloride (as NaCl) 550 mg. per cent; total protein 5·3 g. per cent; albumin 2 g. per cent; globulin 3·3 g. per cent; serum bilirubin 5·6 mg. per cent.

Catheter Specimen Urine

pH 6; Albumin, small amount; some pus cells, no casts.

Intravenous therapy with a 10 per cent dextrose solution containing parentrovite was commenced and aureomycin (500 mg. *statim* and 250 mg. 6-hourly) was given with minimal amount of water for swallowing despite the vomiting. On this regime the vomiting decreased in frequency though the general condition remained unchanged and the jaundice deepened. The urinary output was satisfactory and at the end of 12 hours the urine was acetone free.

Fourteen hours after admission labour commenced spontaneously. When the membranes ruptured, the liquor was seen to be heavily stained with meconium and the foetal heart slowed appreciably but returned to normal on administering intra-nasal oxygen to the patient. A pelvic examination at this time showed the cervix to be very thin and some 3–4 fingers dilated. She was given pethidine, 150 mg. and Synkavit 20 mg. Four and a half hours after the commencement of labour she was delivered by low forceps under minimal local anaesthesia (pudendal nerve block) of a living female child. The third stage was normal and the loss only 6 ounces. Shortly after delivery the blood biochemistry was repeated and reported on as follows:

Blood Biochemistry

Blood urea 55 mg. per cent; blood sugar 125 mg. per cent; serum bilirubin 8 mg. per cent; sodium 265 mg. per cent; potassium 12·0 mg. per cent; chloride (as NaCl) 555 mg. per cent; serum alk phosphatase 44·5 K.A. units; thymol turbidity 4·5 units.

The intravenous drip of 10 per cent dextrose was continued and now Neomycin 2 g. every 6 hours was given orally replacing the Aureomycin. Treatment with neomycin together with the absence of protein from the diet was based on evidence that nitrogenous compounds of intestinal origin are a cause of neuro-psychiatric disorder in hepatic coma or pre-coma (Summerskill, 1958).

Approximately 2 hours after delivery she had a slight brisk post-partum haemorrhage and it was noted that the blood lost showed a lowered tendency to clot. Therefore, 50 mg. of soluble vitamin K were added to the drip bottle and 0·5 mg. of ergometrine given intravenously. After a further 2 hours, she had another heavier loss during which she became shocked and she was transfused with 2 pints of blood, each containing 0·5 mg. ergometrine as the uterus tended to become flabby. Oxygen was also given intranasally.

To rectify the calorie requirement since admission she was given 100 ml. of 50 per cent dextrose intravenously and as sedation was given 5 ml. of paraldehyde intramuscularly.

It was observed that during the first 24 hours since admission there was some weakness and irregularity in the pulse possibly due to the low potassium value in the blood, but this was not shown on electrocardiography.

On the 21st March, 1959, the blood urea was estimated at 50 mg. per cent and the serum bilirubin at 7·5 mg. per cent. Her general condition remained *in statu quo*. The vomiting was less and as there was no dehydration the intravenous drip was discontinued. She was, however, again given 100 ml. of 50 per cent dextrose together with parentrovite intravenously and was now allowed small sips of glucose water.

On the 22nd March, 1959, a full blood count was performed and the blood biochemistry repeated and the reports were as follows:

Blood Count

Haemoglobin 76 per cent; red cells 3,600,000 per c.cm.; colour index 1·0; white cells 30,000 per c.cm.; polymorphonuclear cells 73 per cent; lymphocytes 18 per cent; monocytes 7 per cent;

eosinophils 2 per cent; reticulocyte count 2·5 per cent. There were 10 nucleated red cells per 100 white cells.

Blood Biochemistry

Sodium 315 mg. per cent; potassium 12·8 mg. per cent; serum bilirubin 8·5 mg. per cent; chlorides (as NaCl) 480 mg. per cent.

In view of the continued low potassium values, she was given 2 g. of potassium chloride orally. On the 23rd March, 1959, she was less nauseated but the cerebration was somewhat impaired on one or two occasions. The haemoglobin was 70 per cent of normal and the blood biochemistry values were: blood urea 90 mg. per cent; blood sugar 105 mg. per cent; sodium 320 mg. per cent; potassium 14·0 mg. per cent; chloride (as NaCl) 605 mg. per cent; serum bilirubin 8·7 mg. per cent.

Two days later she commenced a carbohydrate diet and became more alert and cheerful; the jaundice seemed a little deeper, but there was no purpura. Her blood biochemistry began to show improvement though the serum potassium still remained low. The blood biochemistry for the 25th March, 1959, read: blood urea 40 mg. per cent; sodium 315 mg. per cent; potassium 12·5 mg. per cent; chloride (as NaCl) 545 mg. per cent; serum bilirubin 7·0 mg. per cent.

By the 28th March, 1959, the jaundice was fading and she was much improved though anaemic (haemoglobin 56 per cent of normal). On that day also she completed her course of Neomycin. Biochemical analysis of her blood showed: blood urea 15 mg. per cent; serum bilirubin 3·5 mg. per cent; sodium 350 mg. per cent; potassium 16·0 mg. per cent; chloride (as NaCl) 605 mg. per cent.

She continued to improve and on 31st March, 1959, she was allowed to have an addition to her diet of 20 g. of protein as all protein had been withheld since admission (the value of the lipotrophes, choline and methionine, in the acute fatty liver of pregnancy has yet to be determined, as there is as yet insufficient evidence to support the view that this disease is caused by lipotrophe deficiency). Her blood biochemistry again showed improvement and was reported: blood urea 15 mg. per cent; serum bilirubin 1·3 mg. per cent; sodium 305 mg. per cent; potassium 17 mg. per cent; chloride (as NaCl) 635 mg. per cent.

Bed rest was maintained for 3 weeks and lactation depressed with stilboestrol. The anaemia was treated with mist. ferrous sulph., ii drachms, t.d.s. and later with Colliron, ii drachms, t.d.s.

On the 7th April, 1959, liver function tests were performed and showed improvement: thymol turbidity 2·8 units; serum alkaline phosphatase 5·8 K.A. units; serum bilirubin 0·5 mg. per cent.

On 17th April, 1959, she was allowed 60 g. protein in the diet and allowed up for more time each day. She was finally discharged on a normal diet some 5 weeks after admission, with instructions to restrict her activity as much as possible and not to become pregnant again for at least 4 years, and to this end was seen at the Birth Control Clinic. Her liver function test values at the time of discharge were as follows: thymol turbidity 3·2 units; serum alkaline phosphatase 6·0 K.A. units; serum bilirubin 0·3 mg. per cent; and her haemoglobin had increased to 62 cent of normal.

Summary

(1) A case of obstetrical acute yellow atrophy is described.

(2) This condition is in most cases fatal either to mother, foetus or both. In the above case both were discharged alive and well, the former on a full normal diet.

(3) Neomycin was used in large doses in an attempt to sterilize the gut in order to prevent auto-intoxication of the liver and central nervous system.

Acknowledgments

I am indebted to Mr. S. B. Herd, Consultant Obstetrician and Gynaecologist, for permission to publish the case, to Mr. J. K. Wilson, and to Drs. S. Cope and P. C. Chaudhury for much helpful advice.

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THE INCIDENCE OF *STAPHYLOCOCCUS PYOGENES* IN NORMAL HUMAN BREAST MILK

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IN the monograph by Elek (1959) it is stated that the milk of over 90 per cent of lactating mothers contains coagulase positive staphylococci, the authority given being a paper by Duncan and Walker (1942). As this did not seem to tally with the general impression of the incidence of *Staph. pyogenes* in breast milk in this hospital a small survey was undertaken to test the truth of this contention.

METHODS

The nipple was cleaned with 70 per cent alcohol and dried. Milk was then expressed manually, the first few drops being discarded and then a few drops of "mid-stream" milk collected in a sterile universal container and examined in the laboratory within half an hour.

Initially a loopful of milk was spread over a blood agar plate which was incubated overnight aerobically and colonies of *Staph. pyogenes* and *Staph. albus* identified by colonial appearance and slide coagulase test. At a later stage in the survey it was decided to count the number of staphylococci present in the milk. This was done by spreading a 1/50 ml. drop of milk on a blood agar plate and counting the colonies after incubation.

RESULTS

Unselected samples of breast milk from 100 normal lactating mothers between the 4th and 10th day post-partum were examined. *Staph. pyogenes* was found in 4 cases and *Staph. albus* in 47. Counts of *Staph. albus* varied between 100 and 40,000 per ml. but the majority showed less than 1,000 per ml.

Counts were done on 3 of the 4 *Staph. pyogenes* infected cases and showed 700, 1,400 and 20,000 organisms per ml. The case with the highest count was in fact suffering from a slightly sore nipple and milk taken from the other breast was sterile. This case should therefore not be counted in assessing the incidence of *Staph. pyogenes* in normal breast milk.

DISCUSSION

Reference to the original paper of Duncan and Walker suggests that the discrepancy between their results and our own may, at least partially, be explained by differences in technique. Duncan and Walker did not collect their own specimens of milk but swabs were taken by the maternity ward staff and transmitted to the laboratory with about a 20-hour delay before examination. After cleaning the nipple with sterile water swabs were taken of manually expressed milk without touching the skin. Moreover, their technique for the coagulase test was not a conventional one and they even state that some *Staph. albus* give a positive coagulase test. It is considered that the high incidence of *Staph. pyogenes* obtained by

Duncan and Walker may be partly a reflection of skin carriage on the nipple with multiplications of a staphylococcus, present almost by accident, on the milk soaked swab during the period before examination. It is doubtful if even this would account for a 90 per cent carrier rate but perhaps the remainder might be accounted for by their coagulase test technique. Duncan and Walker suggest on the basis of serological typing that the breast milk becomes infected with staphylococci from those present in the noses and throats of babies, and on general grounds this would seem very likely to occur. However, swabbing of the nose, throat, umbilicus and rectum of the babies of our 4 infected cases with phage typing of all *Staph. pyogenes* isolated did not confirm this mode of infection in any case. Nor did it seem that mothers had infected themselves, all being nasal carriers but of different phage types. By a process of exclusion, therefore, it seems that our mothers were infected either by their attendants or indirectly from the ward environment.

Summary

The incidence of *Staph. pyogenes* in normal breast milk is around 3 per cent and not 90 per cent as has been stated.

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CUSHING'S SYNDROME AND PREGNANCY

BY

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SUCCESSFUL pregnancy following adrenalectomy for Cushing's syndrome is rare and only 7 instances have been reported (Hunt and McConahey, 1953; Hernberg, 1955; Worner and Mathew, 1956; Møller, 1957; Tivenius, 1959). An eighth case is described with notes of the management of pregnancy, labour and puerperium, together with a brief review of the literature.

CASE HISTORY

Mrs. D., a housewife aged 24, was first seen in October, 1954 by one of us (G.I.M.S.) complaining of an increase in weight of 2 stones and of irregular periods during the past 6 years, increased growth of hair on the face for 3 years, a 10-weeks miscarriage in 1953, and of headaches and breathlessness for a year. She had a round, ruddy face, obesity of the trunk with a pad of fat over the lower cervical spines, no striae but a considerable growth of hair on the upper lip, face and chin (Figs. 1, 2, 3 and 4). The blood pressure was 170/110 mm. Hg, the fundi and heart were normal and there was no oedema. X-rays showed a normal pituitary fossa, some slight generalized osteoporosis, and tomograms after perirenal oxygen insufflation demonstrated bilateral adrenal hyperplasia. The significant clinicopathological determinations were as follows: Hb. 110 per cent; blood urea 27 mg./100 ml.; with a clearance of 110 per cent; plasma electrolytes, sodium 145–153 mEq./l., potassium 4·5 mEq./l., bicarbonate 27 mEq./l. There was no glycosuria and the glucose tolerance test was normal. The 17-ketosteroids were 20, 22·5 and 19 mg./24 hr. and the 17-ketogenic steroids 27 and 21 mg./24 hr. Corticotrophin gel test: 100 mg. corticotrophin gel were given daily for 3 days. The excretion of 17-ketosteroids increased from 19 to 73·4 g./24 hr. Cortisone suppression test: 100 mg. of cortisone was given daily by mouth for 3 days. The 17-ketosteroids fell from 20 to 14 mg./24 hr. These tests were interpreted as being compatible with the diagnosis of bilateral adrenal hyperplasia, and as being against that of an adrenal cortical tumour.

Accordingly, bilateral adrenalectomy (one stage posterior approach) was performed by Mr. Bernard Harries on 20th December, 1954. The left adrenal was removed completely and a small nubbin (1 cm. in diameter) of the right adrenal was deliberately left *in situ*. The postoperative course was uneventful and the patient was subsequently maintained on 37·5 mg. of cortisone and 5 g. of extra salt a day. During the next 9 months she lost 26 pounds in weight; the body configuration returned to normal, as did the distribution of the facial and body hair (Figs. 5, 6, 7 and 8). The blood pressure fell

from 170/110 to 120/70. Menstruation recommenced 4 months after the operation.

The patient was readmitted on 28th March, 1956 to test the function of the right adrenal remnant. The cortisone was withdrawn and corticotrophin gel 80 mg./day was given for 10 days. During this time she felt cold, weak and nauseated, and the blood pressure fell to 100/60. The eosinophil count rose from 80 to 200/c.mm. However, the plasma electrolyte concentrations did not change significantly and the blood urea did not rise above 30 mg./100 ml. During this time the highest figures for the excretion of 17-ketosteroids were 3·5 and 2·3 mg./24 hr. and for 17-ketogenic steroids 3·3 mg./24 hr. There was a gross delay in the excretion of a water load. The glucose tolerance test gave a low flat curve. From these tests it was considered that there was very little if any function of the right adrenal remnant. The patient was therefore subsequently maintained on oral cortisone acetate 37·5 mg./day and desoxycorticosterone acetate (D.C.A.) linguets 1 mg./day; with this treatment she continued in excellent health. In November, 1956 she developed amenorrhoea and a Friedman pregnancy test was positive.

Management of Pregnancy

The patient's maintenance therapy was continued and she remained very well with a normal blood pressure, while monthly determinations of the serum electrolytes showed no abnormality. She was admitted to hospital at 36 weeks, because the blood pressure had risen to 140/90, there was slight swelling of the fingers and face, and some return of facial hirsuties. For this reason the D.C.A. linguets were discontinued, and the blood pressure promptly fell to 130/80 and the oedema disappeared.

By term, the diastolic blood pressure had risen to 90 mm.Hg and when 7 days over the estimated date of delivery an intravenous pitocin drip was successful in establishing labour. On this day she was given 100 mg. cortisone acetate by mouth and this was repeated the following morning. After a labour lasting 19 hours, she was delivered spontaneously of a living male infant weighing 7 pounds 10 ounces. The third stage was normal with minimal blood loss. The placenta and membranes were complete. The patient was very anxious to breast feed and lactation was satisfactorily established.

For 7 days the dose of cortisone was 75 mg./day. This was reduced to a maintenance dose of 37·5 mg./day with D.C.A. linguets 1 mg./day.

On the 14th day, lactation was suppressed because a small superficial abscess was developing in the right breast. This was treated with aureomycin and incision. She was discharged 5 weeks after delivery, the infant gaining weight on National Dried Milk.

Discussion

Pregnancy is uncommon with Cushing's syndrome and rarely goes to full term. The present patient had manifestations of the disease when she conceived in 1953, the pregnancy ending in abortion at 10 weeks.

Bishop (1954) states that Cushing's syndrome occurs three times as often in women as in men and most frequently between the ages of fifteen and 35. Moreover, it is well known that during pregnancy obesity, mild hirsutism and renal glycosuria may occur. Pregnancy may, in fact, be a predisposing factor to this disease.

In the Guy's series (Bishop, 1954) three patients had Cushing's syndrome with pregnancy and in 2 this had an adverse effect. Cope and Raker (1955) reported that, in their series of 36 female cases, 3 patients conceived and bore children during the active phase of the disease. The gonads of the first 10 female cases operated upon were examined and showed gross atrophy.

The most detailed report with regard to pregnancy and Cushing's syndrome comes from the Mayo Clinic by Hunt and McConahey (1953), who described 7 pregnancies in 4 patients with developing Cushing's syndrome. These resulted in 4 live births, 1 stillbirth, 1 neonatal death and 1 abortion. In 3 cases adrenal hyperplasia was found at operation and, in the fourth, an adrenal cortical tumour was excised. Only their first case required maintenance doses of cortisone and post-operatively a subsequent pregnancy ended in abortion. There were live births in 3 cases following partial bilateral adrenalectomy for Cushing's syndrome. These required no post-operative cortisone.

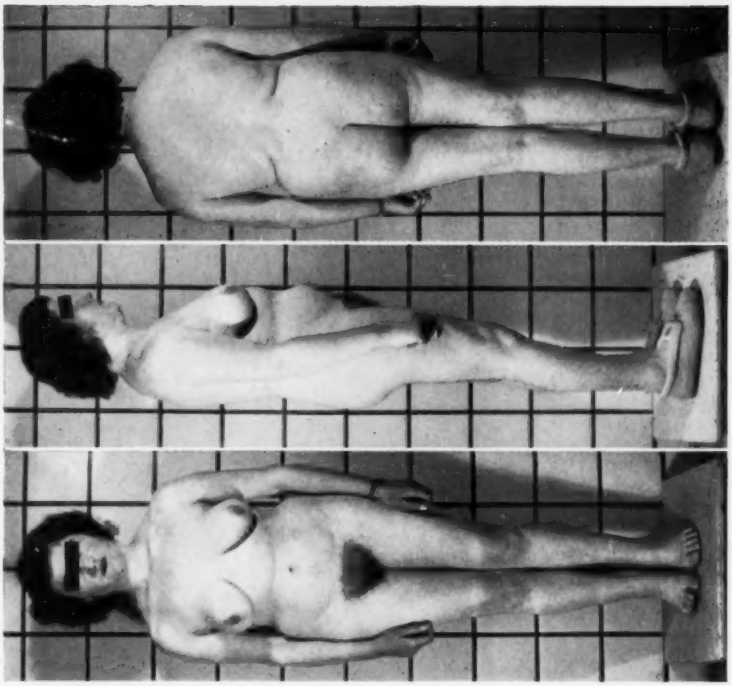

FIG. 4

FIG. 3

FIG. 2

FIG. 1

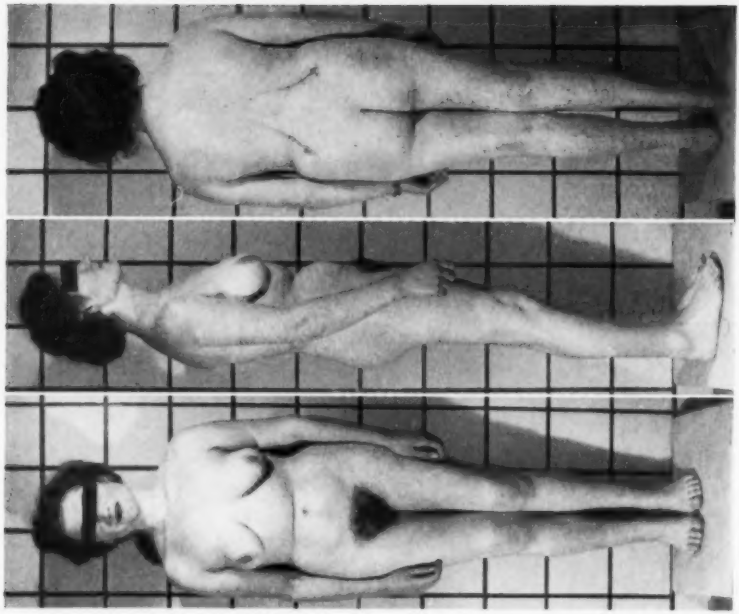

FIG. 8 FIG. 7 FIG. 6

FIG. 5

W.G.MACG., A.G.S., G.I.M.S.

Three cases of Cushing's syndrome treated by adrenalectomy and maintained on cortisone during successful pregnancies have been reported by Worner and Mathew (1956), Møller (1957) and Tivenius (1959).

In earlier reports there are long discussions on the development of "shock" during labour or shortly after. This can be prevented by increasing the cortisone to 100 mg. every 8 hours during the labour and first 24 hours of the puerperium. Should an acute adrenal insufficiency state develop the logical treatment would be by the administration of intravenous hydrocortisone hemisuccinate and not by blood transfusion or by a noradrenaline infusion. Noradrenaline should be used with caution prior to delivery of the foetus because Garrett (1954) has clearly demonstrated that noradrenaline increases the frequency and usually the amplitude of uterine contractions.

Addendum

Since this paper was submitted for publication, Greenblatt, Scarpa-Smith and Metts (1959), have reported 3 cases of Cushing's syndrome with 4 successful pregnancies following surgical removal of adrenal neoplasms.

We wish to thank Professors M. L. Rosenheim and W. C. W. Nixon of University College Hospital for permission to publish this case, and Mr. A. C. Lees of the University College Hospital Photographic Department for the illustrations.

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SIMULTANEOUS TUBAL AND INTERSTITIAL PREGNANCY

BY

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GREENHILL (1956) in summarizing an article on combined intra-uterine and extra-uterine pregnancy, stated that there had been 421 cases of this kind reported. Bilateral tubal pregnancy is well known (Moir, 1956), but interstitial pregnancy is relatively uncommon. Wynne (1929) found 40 interstitial pregnancies in 2,405 ectopics, an incidence of 1·66 per cent. The following case is therefore very rare. In brief, an unruptured left tubal pregnancy was removed on 1st August, 1957, and 40 days later a ruptured right interstitial pregnancy was removed by high subtotal hysterectomy.

CASE HISTORY

The patient, a Nigerian aged 30, was referred to hospital by Dr. J. Gottlieb with a diagnosis of left ectopic pregnancy. The history and findings were classical. The last normal period of 5 days had been on 16th May. There had been a slight loss of 2 days on 14th June. When seen on 31st July she had therefore missed a period in the middle of July. Five days before being seen she had had sudden sharp pain in the left iliac fossa and had felt faint. There was no vaginal blood loss or discharge.

Vaginally, to the left of the slightly enlarged uterus, was a tender swelling.

She had had two children, aged 7 and 4 years at that time, and two miscarriages at 6 weeks in 1955 and 1956, neither of which had been complicated in any way.

Her general condition was good and haemoglobin 74 per cent.

At laparotomy the left tube was found to contain an unruptured ectopic pregnancy in the ampullary portion. Left salpingectomy was performed. The right tube and ovary, and the left ovary, were normal. The uterus was normal in shape but as it was enlarged it was thought there was probably an intra-uterine pregnancy as well.

Recovery was uneventful and she went home on the 10th post-operative day.

On 2nd October she was worried because she had had no "periods" since the operation. She had no pain, but complained of a "hardness" in the abdomen. The natural conclusion was that an intra-uterine pregnancy was continuing, but it was a surprise to find a pelvic tumour rising as high as the umbilicus, for from the operation findings the uterus should only have been just easily palpable above the symphysis. The tumour did not feel asymmetrical.

An X-ray showed no foetal parts. A biological pregnancy test was positive. No pelvic tumours other than pregnancy could have grown so quickly, so it was decided to await events.

One week later she was carried into the hospital in a collapsed state. She was virtually unconscious, so that a history was unobtainable. The abdomen was tumid and tender and there was a little vaginal bleeding. A diagnosis of intra-peritoneal haemorrhage was obvious, but the source of the bleeding was obscure, since 40 days previously the pelvis had been seen to be normal.

Laparotomy was performed after an infusion of 2 pints of Dextran and 4 pints of blood, given in about 50 minutes. About 4 to 5 pints of blood were found in the peritoneal cavity. A foetus aged approximately 16–18 weeks was lying free amid the bowel, and so was its placenta.

At the right of the fundus of the uterus was a ragged bleeding area. The outer two-thirds of the right tube were hanging from the lower

aspect of this area by a thin strand of peritoneum. Its inner third was completely disrupted. It seemed that no reasonable plastic repair could restore tubal patency on the right side and since the left tube had previously been removed, a subtotal hysterectomy was done. The amputation of the corpus was high in order to leave some menstrual function, as this was deemed advisable in one of her age and nationality.

She made an uneventful recovery. Two months later she was very well and had had a 2-day menstrual loss on 22nd November. She failed to return for a further follow-up examination.

Discussion

The interest of this case is that the interstitial pregnancy was not diagnosed at the laparotomy for left tubal pregnancy. The coincident pregnancy was thought to be intra-uterine. The experience of Hyams (1953) throws light on this. He had a patient with 9-weeks amenorrhoea and 8-weeks intermittent severe abdominal pain and moderate vaginal discharge. During a vaginal examination the uterus felt normal in shape until it contracted, when pain was felt and a lump became palpable at the cornu. Incision over this lump revealed the placenta and other products of conception. This was an interstitial pregnancy which was only manifest on the external surface of the uterus during a contraction.

In my case it seems that at the first operation the uterus was relaxed and so appeared normal. If it had been seen to contract or perhaps made to do so by manipulation, it is possible that the interstitial pregnancy would have been seen as a bulge on the uterus.

It may be reasonable to suggest that if at laparotomy for a tubal pregnancy it is thought that there is an intra-uterine pregnancy as well, the uterus should be seen to contract before closing the abdomen.

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LE FORT'S OPERATION

BY

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THREE circumstances have moved me to publish this account of 21 Le Fort operations performed in the last 10 years. The first was the reading of a paper by McKim McCullagh (1955) entitled "Vaginal Plug for Procidentia in Elderly Women".

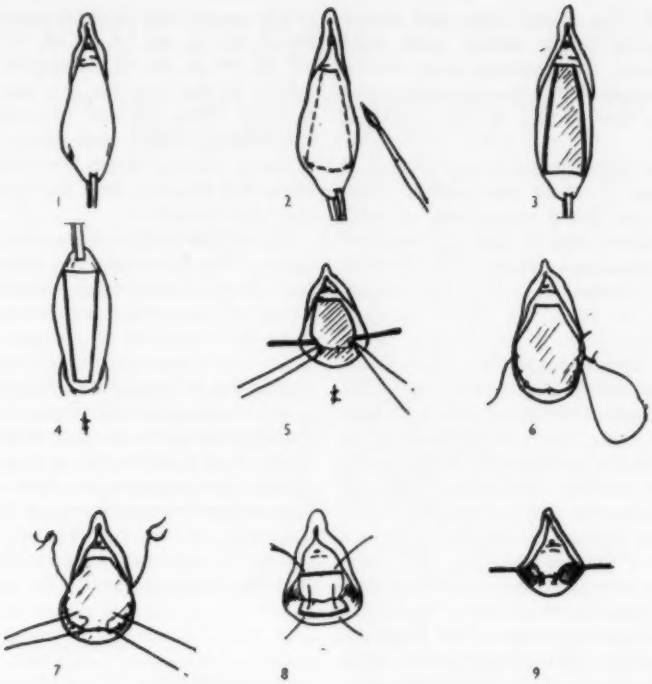
This paper describes a device made of clear perspex which is inserted on rising and can be removed at night and is intended for women "who cannot retain a pessary or who are too old or too ill for operation". Daily oestrogen therapy was advocated. Daily cleansing was necessary and annual replacement of the rubber attachments was required. In one case the "procidentia was so wide that the plug kept coming out". An especially large plug "almost jam-pot size" was therefore made and was a complete success. The ages of his patients were 89, 81, 80, 73 and 72.

Old age we know brings its troubles and one must accept spectacles, the hearing aids, the walking sticks, but surely it is not necessary to inflict the vaginal plug or any other form of pessary on the aged when we have Le Fort's operation instead. Very often, no doubt, the patient can look after these things herself, but 3 of my patients are no longer mentally alert and are in fact in Old People's Homes. Two new patients not in this series are in-patients in a mental hospital, so that the less nursing care and attention they require the better for everyone.

It is probably fair to say that if a woman is fit enough to be up and about in her house, she is fit enough to stand this relatively minor operation. If she is bed-ridden, she may not need any help at all. There was one bed-ridden patient in this series and she was in very miserable circumstances. In addition to being 88 and enormously fat, she had a huge procidentia. She had incontinence of micturition and poor control of the bowel. I did her operation under local anaesthesia but she died shortly after of uraemia and at autopsy was found to have bilateral renal calculi. She was living in great misery and I doubt if her operation appreciably shortened her life. It may have been a blessing to her and her relatives.

The second circumstance was the correcting of examination papers at a university centre when the treatment of procidentia was asked. No mention of Le Fort was made in any answer. On mentioning this to my two co-examiners, both holders of university chairs, I was told that this operation "had no place in modern gynaecology". With this opinion I certainly disagree and Speert (1958) of the Presbyterian Hospital, New York, supports me in my belief, stating that "the simplicity and safety of the operation still commend it for correction of uterine prolapse in the elderly and poor-risk patient". In the elderly and poor-risk patient, an extensive pelvic floor repair with extensive anterior and posterior colporrhaphy with or without vaginal hysterectomy must inevitably be more dangerous; the blood loss is greater, the shock is greater and the time taken is much longer. Le Fort's operation can be performed in 20 minutes with minimal blood loss and the patients give my anaesthetists, Dr. Gleadow and Dr. Condon, no apprehension at all.

The third circumstance is that the Senior Registrar of today has not seen the operation performed; newly qualified doctors have not even heard of the operation, so that in a very short time we shall lose this very valuable geriatric operation.



FIGS. 1 to 9

Le Fort's original operation, performed in 1876, was reported in 1877. He removed a strip of vaginal epithelium 6 cm. long and 2 cm. wide. Then, replacing the uterus, he united the denuded area with interrupted silver thread sutures and thereafter the lateral edges also with silver wire.

The operation I perform is modified in many ways from Le Fort's original method. After cleaning the operation site, 10–20 ml. of adrenalin 1: 100,000 in saline is infiltrated beneath the skin, in front and behind.

The strips of vaginal epithelium removed are wedge shaped, not rectangular; this is important. At the fornix the transverse incision, placed about 1½ cm. from the os, extends to 1 cm. from the edge of the protrusion. Its actual length will vary with the size of the procidentia. It is usually about 5 cm. The lower transverse incision measures 2 cm. in length. It is important to place this incision at the level of the neck of the bladder (Figs. 2, 3 and 4). If it is carried lower than this then the drag of the posterior wall might pull the urethra open and produce stress incontinence.

It is essential to draw the proposed lines of incision first (Fig. 2). Having marked out the area in front, the area to be removed on the other aspect can now be delineated. In this way only can we guard against taking off too much or too little. The drawing can be done with a paint brush, but a Playfair's probe covered with wool and dipped in Bonney's blue serves excellently.

Secondly, Number 1 catgut is used throughout. Three interrupted stitches unite the transverse incisions (these are passed so as to invert the edges and to leave the knots on the epithelial

surface, Fig. 5). The lateral edges are united with a continuous catgut suture, each third stitch being locked. These stitches must also be passed from the epithelial to the raw surface and back from the raw surface to the epithelial surface (Fig. 6).

When the first three stitches on each side have been passed, two or three intermediate interrupted stitches are placed transversely to unite the two raw surfaces (Fig. 7). The raw areas are dusted with penicillin-sulphonamide powder, the protrusion is pushed in and the transversely placed stitches are tied. The lateral stitching recommences and 3 or 4 cm. further down another pair of interrupted stitches, transversely disposed, is passed. A little more powdering, more pushing back of the protrusion and these stitches too are tied. The lateral stitching continues to the end. The operation is completed by a stitch in the midline to join anterior and posterior walls together (Figs. 8 and 9).

The only post-operative treatment given is a daily irrigation of the two channels with Eusol. The patients are out of bed on the day after operation and can return home in from 10–14 days.

If there is a marked hernia of the Pouch of Douglas or a very deficient perineum, these things can be dealt with at the appropriate time.

The drawings executed by my Registrar, Miss Joan Curtis, illustrate the steps of the operation.

The impression must not be taken that Le Fort's operation is being recommended instead of pelvic floor repair with or without vaginal hysterectomy. During 4 years in which total figures are to hand, Le Fort's operation was performed on 11 occasions while the total of other major repair operations was 278. It is reserved for the old and the frail and one may be frail without being very old, and only in those patients for whom the function of the vagina is no longer important. It is an alternative to pessary treatment.

The ages of the patients operated upon were 58, 59, 61, 62, 62, 65, 65, 65, 67, 68, 73, 75, 75, 77, 78, 79, 80, 80, 82, 84 and 88. As mentioned earlier in the text, the old lady of 88 died in hospital. There was one other failure, due to an insufficiently wide strip being removed; the prolapse recurred down one of the two vaginae. None has recurred since the wedge-shaped area has been excised.

Two of the patients have since died of natural causes. Two have been lost sight of. Those who have been followed up are comfortable, have no bowel or micturition symptoms, nor do they have any sensation of prolapse. The uterus in every case is supported in its correct position by a solid bar of living tissue 3 inches long.

In conclusion therefore, I deplore that Napier pessaries and McCullagh plugs are still being used, I regret that it is being taught that there is no room for this operation and I urge the younger gynaecologists to gain a personal experience of this operation to learn how easy it is and to appreciate how satisfied the patients and their practitioners will be with the results.

Summary

A modification of Le Fort's operation is described.

This operation will cure any procidentia however gross.

It is the shortest and the simplest and therefore the safest method of achieving this object.

By this operation the aged are spared the inconvenience and unpleasantness of the pessary life.

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EXTENDED USE OF THE LE FORT OPERATION FOR VAGINAL PROLAPSE IN THE ELDERLY

BY

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A SEVERE or complete procidentia is fairly common in elderly women and is a cause of serious discomfort and incapacity. While lying down there may be little prolapse but as soon as the patient gets to her feet the cervix drops and as the day proceeds the protruding mass gets larger and lower so that sitting is very uncomfortable and walking a painful process. The projecting cervix rubs on the thighs and underwear becoming eroded and in some cases epidermoid carcinoma develops in the eroded area. Discharge with bleeding and soiling of the underwear is common. Micturition is rarely affected but in some cases the patient has to replace her prolapse manually before she can empty her bladder.

With the increase in longevity more and more women over the age of 65 consult us about their prolapses. Many are robust and active but many have varying disabilities chiefly cardiac or arthritic which make anaesthesia and surgery a hazard. All are made happier, more comfortable and more active if their prolapses can be cured.

The use of supporting pessaries is far from an ideal solution to the problem. Elderly patients find the care of these by douching or frequent bathing a burden and if they are arthritic such care is almost impossible without the daily attendance of a nurse. Renewal at regular intervals is a necessary and expensive part of such treatment. Prolonged wearing of such a support also increases the risk of malignant change in the vaginal mucosa. The newer materials such as polythene are better than the old in all respects but these elderly ladies are really better from the comfort and health points of view without any "foreign body" in the vagina. In not a few of course it is difficult if not impossible to find any support which will stay in position comfortably.

In the area where I work there are a large number of such patients who have settled here on retirement, both married and single. In the six years 1952–1958 I saw 295 women over the age of 60 with this disability. In some cases, especially the single and nulliparous women, there was a simple vault prolapse, in others there was associated cystocele and rectocele, and in some there was cystocele or rectocele or the two combined but no prolapse of the cervix or vaginal vault. Early in this period I realized that a Le Fort type of operation was the simplest and most painfree method of bringing relief to these patients, and I soon found that it was the operation of choice provided the lady was single, widowed or had discontinued sexual intercourse. Most came into these categories. The alternative operative procedures—colporrhaphies of varying types—were more extensive and painful and not infrequently contra-indicated because of the patient's medical condition which made the necessary anaesthesia an unjustifiable risk.

ADVANTAGES OF THE LE FORT OPERATION

Minimal Anaesthesia is Needed. Dr. Lee's comments follow below.

Post-operative Comfort. The post-operative period is practically painless and is trouble-free

so that the old ladies do not have to stay in bed but can use the toilet and look after themselves from the first—a very beneficial thing at this age. There are no micturition difficulties but there is often some frequency and even stress incontinence for a few weeks until the vesical sphincter regains tone. The patients are immediately impressed with the complete comfort of the sitting position especially compared with the pre-operative period. They usually enjoy their stay in hospital thoroughly and regard it as a restful holiday.

Low Recurrence Rate. I have developed certain modifications in technique which have made for better healing and it is now rare for a case not to have sound healing. As the figures show recurrence is also rare—8 cases only have been seen but possibly a few more have occurred.

Choice of Case. All patients over the age of 65 in whom marital life had been discontinued were considered suitable. A few younger widows and spinsters were also included. Prolapse of the vault and/or rectocele, cystocele and hernia of the Pouch of Douglas were operated upon by this technique. The less the vault prolapses the more difficult the operation becomes but with increasing experience all can be done successfully. Thirteen patients residing in the local hospital for mental illness were treated—many by request of the nursing staff who found them easier to look after when the operation had been done.

Medical disorders were rarely a contra-indication as is shown by the survey of cases treated—see below.

Pre-operative Preparation. Rather to my surprise the vaginal mucosa is usually quite vascular and only rarely do I find it wise to use either oestrogens or local acid jellies to prepare the vagina for operation. As a rule the patient is admitted the day before the operation and the only preparation is a simple enema and a vaginal douche of weak Dettol or Roccal. If the prolapse is very large and oedematous with trophic changes in the vaginal mucosa the patient is admitted a week before operation and a course of oestrogens given by mouth, the prolapse being reduced and kept in position by a gauze pack soaked in flavine and paraffin.

Anaesthetic. The majority of these old patients have been anaesthetized by my colleague Dr. J. Alfred Lee, F.F.A., R.C.S. He says: "They receive relatively light premedication which is usually morphine 1/8 gr. with atropine 1/100 gr. A Mitchell needle is inserted into a suitable vein on the dorsum of the hand and a sleep dose of thiopentone is injected. This is usually 75 to 150 mg. and is given in 2·5 per cent solution. The patient is then wheeled into the operating theatre and nitrous oxide with 25 per cent of oxygen is inhaled. Before the legs are elevated a further 100 to 150 mg. of thiopentone is injected and during the operation, which takes between 10 and 20 minutes on average, additional barbiturates may be needed. It is rare to exceed 500 mg. Occasionally in younger patients, those deformed by obesity and those showing abnormal resistance to anaesthesia, minimal trichlorethylene is used to supplement the gas and oxygen, but this is required in less than 20 per cent of the patients. It is very important that the patient's skin should not be stimulated by towel clips or other trauma. The tissues actually operated on in the Le Fort operation do not provoke the active reflex responses which are so characteristic of such operations as the Fothergill repair, and which require much deeper anaesthesia for their suppression. It is usual for these patients to be talking within 5 minutes of the termination of the operation, and as the painful areas of the perineum are not involved, post-operative analgesics are very seldom required. From the anaesthetic point of view, these patients present no greater problem than do those undergoing a dilatation and curettage, an important point in these 70, 80 or 90-year-old patients."

Operative Position. The lithotomy position is used if possible but where there is severe arthritis of the hips and especially if an arthrodesis has been performed the operation is done in the left lateral position or with the two legs held straight in full extension and as far abducted as possible by assistants.

Operative Technique. The vulva and upper thighs are swabbed with Dettol in weak solution and then the anus is similarly cleaned. The vagina is swabbed with the same solution and the bladder emptied by catheter.

The vulva is swabbed dry and a thin layer of mastich painted round the introitus. To this the lithotomy towel is adjusted so that it sticks on to the skin and avoids the use of skin clips which often cause unpleasant lesions in elderly patients and stimulate movement in the lightly anaesthetized. A Landon retractor is employed and the anterior and posterior cervical lips held lightly with Littlewood's forceps. If the cervix is inflamed it is lightly cauterized. If it is seriously eroded then a wide amputation is performed, the lateral vessels being ligated with catgut stitches and the stump covered by mucosal flaps. If there has been any bleeding the uterus is curetted to exclude malignancy. Usually no curettings are obtained, the bleeding being from the eroded cervix. If the cervix is amputated it is sent for section so that malignant change is detected if present. Very rarely is this the case and if so it is early and strictly local so that further treatment is unnecessary, but the patient is carefully followed up. To date no sequelae have occurred in any case.

A longitudinal incision is then made in the midline of the posterior vaginal wall from cervix to perineum and a 3/8-inch flap dissected free on each side. A similar incision is made anteriorly from urethra to cervix and the flaps prepared. If the prolapse is very bulky a strip of mucosa is removed from each aspect in place of the simple incision. The width of strip removed varies with the size of the prolapse—the aim being to leave a double vagina each half of which admits a slim index finger only.

The first catgut stitch joins the apex of one incision to the other across the cervix and will form the upper border of the central antero-posterior vaginal septum beneath the cervix. Subsequent stitches are placed alternately on each side from above downwards joining the anterior to the posterior flaps on each side of the septum (Fig. 1). Each stitch is inserted at right angles to the central incision first on the anterior flap and then on the posterior flap so that when it is tied there is good contact between the two flaps over a full 3/8 inch within the lumen of the new narrow channel (Fig. 2). These stitches are placed alternately on right and left sides at 3/8-inch intervals until the vulva is reached. If the anterior and posterior vaginal walls are unequal

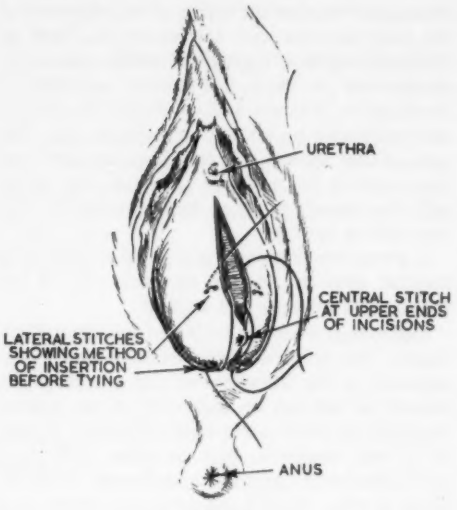

FIG. 1
Method of inserting stitches.

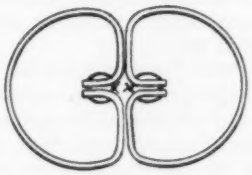

FIG. 2
Transverse section of vagina after operation.

in length, which is quite common, the inter-stitch intervals are adjusted so that the vaginal introitus is reached simultaneously, the stitches on one flap being slightly further apart than those on the other shorter one. The final stitches, one on either side, lie about ½ inch above the urethra anteriorly and the perineal edge posteriorly. No perineorrhaphy is done and no stitches are inserted through the levator ani muscles so that there is no stimulation needing deep anaesthesia and no pain in the post-operative phase. A septum is formed uniting the anterior to the posterior wall in the midline which is about an inch in depth at its lower end. It is not uncommon for considerable oozing to

take place between the layers of the septum and this may interfere with apposition and healing. A 2-inch length of corrugated rubber drain one corrugation in width is therefore inserted for drainage for 36 hours. It is stitched to the septum anteriorly and posteriorly with black silk. The ends of the threads are left 2 inches long and tied together to facilitate removal. The nurse pulls the threads gently to bring the stitches into view before cutting.

A penicillin-sulphonamide powder mixture is inserted into the vagina on each side of the septum and a sterile pad applied.

Differences from Bonney's and American Techniques. This method differs from Bonney's description in the direction of the stitching. He placed the stitches on each side of the septum vertically parallel to the central incision instead of at right angles so that the areas of flaps in apposition were much less and the risk of breakdown greater. He did not drain the septum and so avoid separation of the layers by blood and serum during the immediate post-operative period, and he recommended a perineorrhaphy which required deeper anaesthesia and increased post-operative pain.

In the United States continuous suturing of the lateral flaps to each other is recommended on both right and left sides of the septum instead of the interrupted stitches used here, and central suturing of the sub-vesical to the rectal fascia between the two layers of the septum is employed. I have not found this necessary—the layers knitting firmly without it and the length of the operation being correspondingly diminished.

Post-operative Care. The patient is kept in bed for 36 hours until the septal drain is removed. As already stated sedatives are rarely needed. While in bed the patient is blanket bathed once and the vulva is jug-douched after using the bed pan. Once she can get up she has two warm baths daily and washes herself as she feels the need.

Some vaginal discharge, occasionally blood-stained, occurs for 10 days or longer but the patient is usually dry within 3 weeks. She is kept in hospital for 2 weeks but is not in bed after the first 36 hours. After discharge from hospital she is advised to do no lifting or carrying for another month, when a final examination is made.

TABLE I

Le Fort Operation on Cases of Procidentia at General Hospital, Southend-on-Sea, from 1952 to 1958

Year	No. of Cases	Age Groups		
		60–70	70–80	Above 80
1952	24	15	9	–
1953	39	24	14	1
1954	36	12	24	–
1955	39	14	22	3
1956	41	18	22	1
1957	51	24	24	3
1958	65	24	36	5
Total	295	131	151	13

Survey of Cases Treated. Table I shows the numbers in each age group during each of the 7 years. It will be noticed that more patients of the higher age have been operated upon in more recent years as we have appreciated the possibilities of this operation.

Among the 295 cases there have been 137 with marked hypertension, 16 with heart disease and 10 diabetics all of whom would have given considerable anxiety if any other operative treatment had been employed and many of whom would have been inoperable under such circumstances. In most cases there has been complete comfort after operation apart from some temporary discharge and stress incontinence. In a few the lower end of the septum bulges very slightly but has never actually protruded beyond the labia.

Occurrence of uterine malignancy after operation has happened only once. It was found possible to perform a diagnostic curetting for the post-menopausal bleeding *via* one vagina at the side of the septum. A total hysterectomy was subsequently performed and the patient is alive and well 6 years later.

Recurrence of prolapse has taken place on 8 occasions and resulted from a failure to make the two new vaginas sufficiently narrow, so that the cervix prolapsed again on one side of the septum.

In 2 cases a ventro-fixation was performed with success, in 2 cases the Le Fort operation was repeated with success, in 1 case a vaginal

hysterectomy was performed and in 1 a colpoperineorrhaphy. The remaining 2 were fitted with cup and stem pessaries as they were loath to undergo further operative treatment.

Summary

An extended use of the Le Fort operation for elderly patients with prolapse is described. The choice of cases and advantages of the operation are considered.

Anaesthesia and operative technique are given in detail.

Two hundred and ninety-five cases treated are reviewed.

My thanks are due to my late House Surgeon Dr. Thelma Rasalam, for her help in reviewing the case records and to the Records Officers at the Southend and Runwell Hospitals for their co-operation.

A CASE OF CHRONIC HYPERTROPHIC VULVITIS

BY

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MRS. P.C., aged 43 years, was seen in May, 1956, in the Gynaecological Out-Patient Department, complaining of periodic swelling and irritation of the vulva for 1 year. The periodic vulval swelling involved both labia majora and when it occurred there was associated pruritus vulvae with an increased white vaginal discharge. The swelling had no relation to the menstrual cycle and lasted for 2 to 3 days, after which it gradually subsided. The frequency of these episodes was not constant.

Her periods were normal and regular and there was no excess vaginal discharge, except during the above mentioned episodes. She was married with two children and had had no previous abortions. She had never been abroad nor had any serious illness or operations in the past.

On examination the patient was well built and nourished. There was no abnormality noted in the respiratory and cardiovascular systems. Her blood pressure was 120/80 mm. Hg. No abnormality was noted on abdominal examination.

On vaginal examination there was marked hypertrophy of both labia majora, with gross nodular thickening of the skin (Fig. 1). There was no excessive vaginal discharge noted. No abnormality was found in the uterus, cervix or appendages on bimanual palpation.

This was thought to be a case of elephantiasis vulvae and the patient was investigated as follows:

The Wassermann and Kahn tests and the gonococcal complement fixation reaction were negative. Repeated vaginal smears showed the absence of monilia or *Trichomonas vaginalis*. A vulval swab showed a profuse growth of haemolytic streptococci, sensitive to penicillin, aureomycin, chloromycetin and terramycin. No abnormality was found in the catheter specimens of urine.

Blood: Haemoglobin 11·85 g.; total leucocytes 8,700 per c.mm.; neutrophils 87 per cent, lymphocytes 10 per cent, monocytes 2 per cent, basophils 1 per cent, E.S.R. 50 mm. in 1 hour. No microfilaria were seen in repeated blood films, taken at night. Frei's test was negative.

Vulval biopsy showed the surface of the skin to be thrown into papillomatous folds due to maximal dilatation of superficial lymphatic vessels. The epidermis also showed irregular hyperplasia. The lower cutis showed increase of vessels and a chronic inflammatory reaction, consisting of normal cells and a considerable number of mast cells. The histology showed features as seen in elephantiatic conditions.

TREATMENT

Potassium permanganate 1: 8,000 solution was prescribed for local application to the vulva t.d.s., together with Neomycin cream for local use t.d.s.

FURTHER PROGRESS

The above treatment helped in clearing away the haemolytic streptococcal vulval infection and diminishing the pruritus vulvae, but the hypertrophic nature of the vulva persisted. This did not seem to worry the patient, as long as there was no associated pruritus vulvae. Antihistamine preparations (Anthisan) were also tried locally, but without much effect. Empirical

FIG. 1
Elephantiasis Vulvae.

FIG. 2
After local vulvectomy.

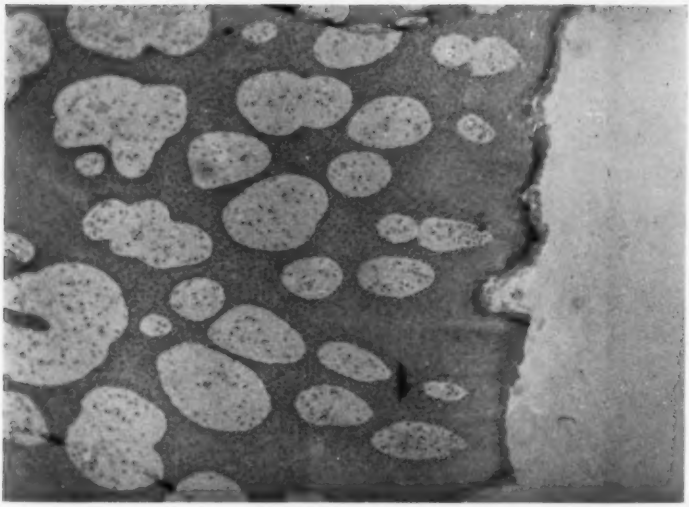

FIG. 3

Marked hypertrophy of epithelial layer with considerable increase in number and size of lymphatics.

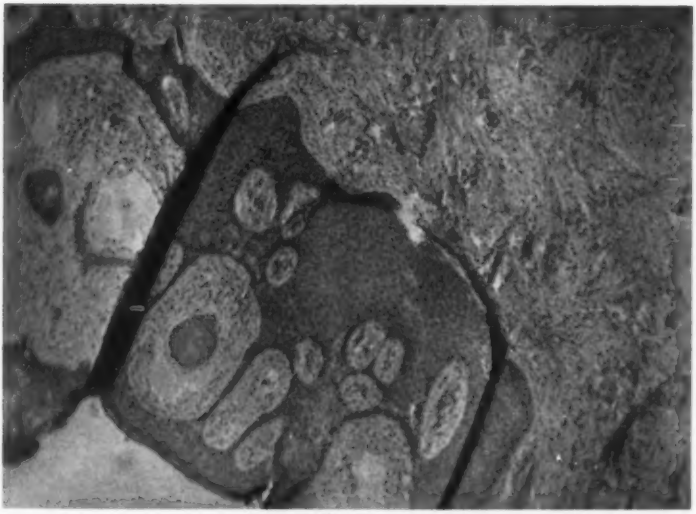

FIG. 4

Thickened and oedematous connective tissue with chronic inflammatory infiltration.

therapy with intramuscular antimony (Anthiomaline) was also tried over a period of 4 weeks without any effect.

After about 6 months of hospital attendance, there was no change in the hypertrophic condition of the labia majora, although the patient did agree that the pruritus vulvae was very much better. Local vulvectomy was considered at that time, but due to the reluctant attitude of the patient this was not insisted upon.

For 2 more years her vulval condition remained the same, and in January, 1959, she agreed to have a vulvectomy done. A local vulvectomy was performed, from which she made an uneventful recovery.

Pathological Report on Vulvectomy Specimen

There were marked hypertrophic changes in the epithelial layer with overgrowth of the papillae, and a marked increase in the number of lymphatic vessels, with considerable dilatation of the same (Fig. 3). The connective tissue was enormously thickened and oedematous with chronic inflammatory infiltration (Fig. 4). This was consistent with the microscopic appearance of elephantiasis vulvae.

Comments

Elephantiasis is considered to be due to blockage of lymphatic vessels, due usually, in the tropics, to the parasitic worm, the *Filaria sanguinis hominis*. In the non-tropical forms of this condition, lymphatic obstruction may be the result of syphilitic lymphangitis or to any form of chronic skin infection.

In this case haemolytic streptococcal infection was noted from a vulval swab taken during the first visit of the patient to the Gynaecological Out-Patient Department. This was presumed to be the cause of the chronic lymphatic obstruction in this case; no other cause could be detected.

Acknowledgments

I am grateful to Mr. K. M. MacKenzie for his help and permission to publish this case, and to Dr. Nicholas for the photomicrographs.

CHORIOADENOMA DESTRUENS

Report of a Case, Investigated by Aortography

BY

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NOVAK AND SEAH (1954) included and discussed chorioadenoma destruens when they reviewed the benign trophoblastic lesions in the Albert Mathieu Chorionepithelioma Registry.

They stated that "malignancy as it occurs in trophoblastic lesions is determined by the microscope as it is in all fields of pathology, and not by the clinical course . . . The microscopic characteristics of choriocarcinoma are now so well established that false negative diagnoses should be rare, i.e., a genuinely malignant tumour will not often be called a benign lesion. The mistakes are almost always in the other direction, a benign lesion being incorrectly diagnosed as choriocarcinoma."

The three main features that characterize a chorioadenoma destruens are as follows:

(1) Marked trophoblastic proliferation.

(2) Local invasion of the depth of the uterine wall, peritoneum and parametrium by this trophoblast. Distant metastases are rare but can occur.

(3) The persistence of the villous pattern in this disease process.

The purpose of this paper is to record a further example of chorioadenoma destruens in which there were unusual features. Extensive metastatic lesions developed rapidly in the lung fields over a period of 2 months. These deposits cleared after treatment by a total hysterectomy with bilateral salpingo-oöphorectomy.

The angiographic pattern of the uterine tumour was studied by serial aortography. The only other references to angiography in hydatidiform mole and chorionepithelioma were by Borell and Fernström (1955, 1958), but no examples of chorioadenoma destruens were included. In his monograph *Arteriography of the Uterine Artery*, Fernström (1955) indicated the value of the examination in obstetrics and gynaecology; but the group of hydatidiform mole, chorioadenoma destruens and chorionepithelioma was not included in the discussion.

The clinical details, copies of radiographs, operative specimen and histological sections were reviewed by the Chairman and Members of the Albert Mathieu Registry (C.R.507) and a report from the Chairman, Dr. John I. Brewer, was of great help and considerable interest.

Case Report

A single girl aged 16 years was admitted on 12th December, 1956, with regular lower abdominal pain and severe bleeding *per vaginam*. A provisional diagnosis of

"incomplete miscarriage" was made by her practitioner.

The patient, a nullipara, was not sure of the date of her last period but thought it was 4 to 5 months previously. While in bed on the night of admission brisk bleeding *per vaginam* began suddenly. She passed several large clots and felt somewhat faint. Her pregnancy had been accompanied by vomiting several times a day, and for the past month she had been coughing up small amounts of bright blood.

Past medical history was unremarkable except for an admission earlier in the year to a psychiatric ward because of overdosage of phenobarbital tablets.

On admission, a flushed young girl of only moderate intelligence presented. The blood pressure was 130/80 mm. of mercury and the pulse was regular, with a rate of 114 per minute and of good volume. The uterus was enlarged to the size of 24-weeks pregnancy, no foetal heart was heard and the vaginal examination revealed a moderate amount of blood clot and the cervical os was closed. There was neither oedema nor evidence of toxaemia. The haemoglobin was 8·2 g. per cent. A diagnosis of "threatened miscarriage and haemoptysis" from septic emboli was made.

Blood transfusion was started and antibiotics, at first penicillin, then seclomycin, were administered. After 48 hours the haemoglobin level was still only 9·0 g. per cent, and blood loss was increasing. Abdominal pains and a heavy bearing-down sensation were experienced and by the evening the patient was bleeding profusely. Radiographs of the abdomen showed no evidence of foetal parts, and the lung fields were clear (Fig. 1). Vaginal examination revealed that the os was still closed, but some vesicles were expressed from the uterus and the diagnosis of "hydatidiform mole" was made. Five units of pitocin were added to 1 pint of blood which was given intravenously at 60 drops per minute. Improved contractions began, the vaginal bleeding became less, and after 5 hours she commenced passing mole and blood clot. Two hours later large amounts of mole had been passed and the blood loss was small. Her general condition was much better, but the haemoglobin level was 7·0 g. per cent, and packed red cells from 3 pints of whole blood were given.

On 16th December, 1956, the vaginal loss had ceased, the pulse was 90–100 per minute and of good volume; the haemoglobin level was 9·0 g. per cent. Further packed red blood cells from 2 pints of blood were given. She had had by now 13 pints of blood. The following day the haemoglobin level was 11·5 g. per cent, the pulse rate 80 per minute. Forty-eight hours later the uterus, which was enlarged to the umbilicus, was evacuated with the patient under a general anaesthetic. A considerable amount of mole was removed by the finger and blunt curette. No enlargement of the ovaries, suggestive of lutein cysts, was detected. The pathologist (J.T.O'B.) reported "The specimen consists of multiple tiny cysts. Histological examination shows cystic degeneration of chorionic villi—hydatidiform mole" (Fig. 2).

Post-operatively, the patient complained of pain in the right side of the abdomen and shoulders, and on examination there was slight rebound tenderness. She was kept under observation and a half-hourly pulse recorded lest rupture of the uterus with intra-peritoneal bleeding had taken place. Further blood was given.

On 21st December, 1956, the haemoglobin was 13·5 g. per cent. The pain became less marked and there was moderate reddish vaginal loss. On Christmas Eve she was discharged home to return in 2 weeks time for a further curettage.

On re-admission there was still a brownish vaginal discharge, and that morning she had coughed up some blood.

A chest radiograph was reported by W.J.W. "There are a number of round opacities in the left and right lung fields. Lobular areas of consolidation are present on the right side. Appearances are those of multiple secondary deposits (Fig. 3). Straight abdomen—a moderate sized soft tissue mass arises from the pelvis." An aortogram was reported: "There is a very vascular mass outlined in the pelvis which retains the opaque medium for several seconds following the injection. This appearance is seen only with chorionepithelioma or mole. In view of the chest findings chorionepithelioma would seem likely here."

A Friedman test was "positive at high dilutions". A further curettage was carried out on 18th January, 1957, when the uterus was the size of 12–14 weeks pregnancy. The right ovary was somewhat enlarged. Fleshy curettings were obtained from the anterior wall of the uterus

near the fundus. Histological examination did not reveal any malignant material. Villi were present. A routine Friedman test was reported positive on 30th January, 1957, but negative results in all dilutions. The sputum was examined on two occasions for *Mycobacterium tuberculosis* and tumour cells with negative results. After a further blood transfusion the patient felt so well that she was discharged home.

The difficulty at this stage was to decide whether to perform a hysterectomy or not. Radiological findings favoured chorionepithelioma. The Friedman test was still positive after 5 or 6 weeks but negative in dilutions. The curettings were benign. It was decided to temporize.

By 28th February, 1957, the routine Friedman test was positive but negative in dilutions. The chest film at this stage showed progression of the disease process over the last 3 weeks (Fig. 4). A further aortogram was carried out and the following points noted: "There is still a large vascular tumour present in the pelvis. There was evidence of arteriovenous shunts in the early and late arterial phases. It is a little less than that seen on 12th January, 1957. The combined appearances are those of chorionepithelioma" (Figs. 5a and 5b).

The patient was readmitted as it was considered that the rapidly proliferating secondary deposits in the lung fields must lead to cor pulmonale from purely mechanical factors. Operation seemed indicated to save the life of the patient. On 8th March, 1957, a total hysterectomy with bilateral salpingo-oöphorectomy was carried out. The liver and peritoneum appeared normal. The patient made an uneventful recovery, and was discharged home 13 days later.

Examination of the specimen showed cystic ovaries and a bulky uterus, with a small soft intramural nodule on the right side of the body (Fig. 6). The histological appearance of this nodule was as follows: "The mucosal surface of the tumour mass is necrotic with collections of large irregular trophoblastic cells infiltrating the muscle wall. These infiltrations occur as small groups of cells and large irregular masses with destruction of muscle and some inflammatory reaction. There are occasional large cysts with much trophoblastic proliferation. In some of these sections tumour is seen within the vessels. The appearances are neoplastic. They are those of chorionepithelioma" (Fig. 7). Figure 8 shows villous pattern demonstrated in sections from operative specimen.

The uterine arteries of the specimen were injected with 50 per cent Diodone. A soft tissue film was taken, which demonstrated the angiographic pattern of tubes, ovaries, uterus and tumour mass (Fig. 9).

Following her discharge the patient has been in excellent health and has gained about a stone in weight and has been back at work full time. The only disturbance has been mild symptoms of hormone imbalance. The metastatic lesions in the chest have gradually decreased in size and at the end of May, 1958, the lung fields were clear (Fig. 10). The routine Friedman test at this stage was still positive but negative in dilution. The final Friedman test (October, 1958) was negative.

Two and a half years after hysterectomy the patient remains in good health—she has no menopausal symptoms and leads a normal life. She was married on 29th August, 1959.

Discussion

In the group of trophoblastic lesions, difficulty frequently occurs in making a distinction between invasive mole (chorionadenoma destruens) and chorionepithelioma. Some cynics would hold that if the patient dies, it was chorionepithelioma; if she lives she had invasive mole. Previous workers note that diagnosis from curettings is hazardous. Our case illustrates this point as the histological finding on the products of curettage on each occasion was hydatidiform mole. Intramural lesions may give the pathologist a diagnosis but this is of little help to the clinician in deciding whether to sacrifice the uterus or not.

From the histological point of view the anaplastic nature of the cells is of little help in coming to a firm diagnosis. Novak (1954) states that the presence of villi is against the diagnosis of chorionepithelioma but does not exclude it. Bettinger (1957) noted that by looking at the trophoblastic cells one cannot decide what this

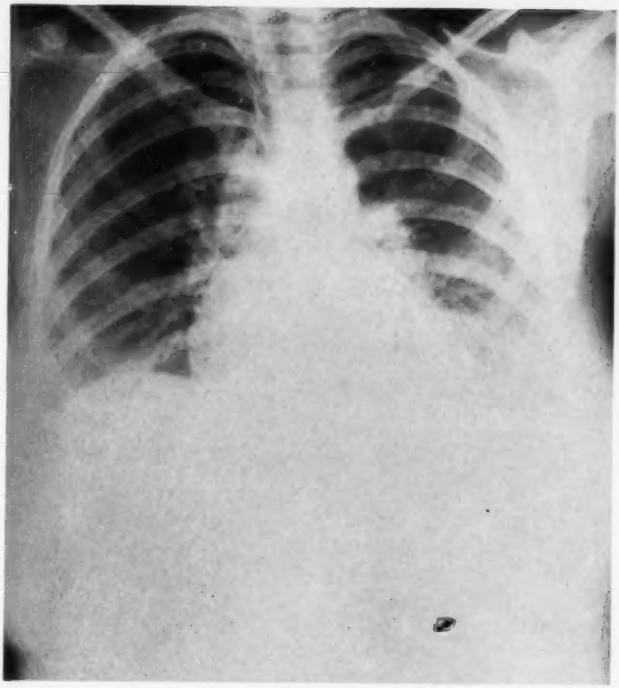

FIG. 1
Radiograph of chest taken on 17th December, 1956, showing no definite evidence of secondary deposits.

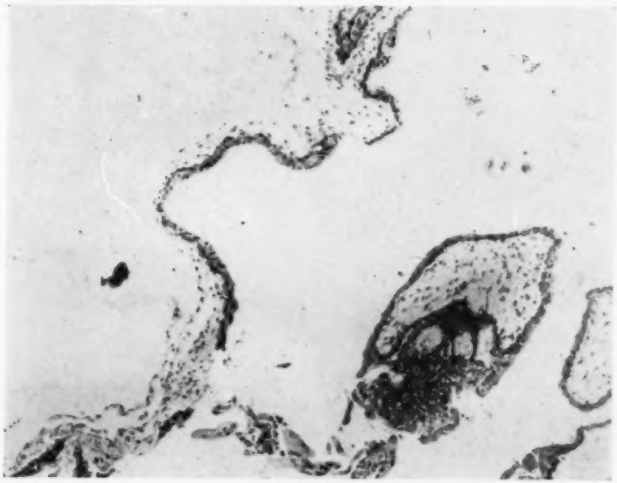

FIG. 2
Original section of hydatidiform mole. ×32.

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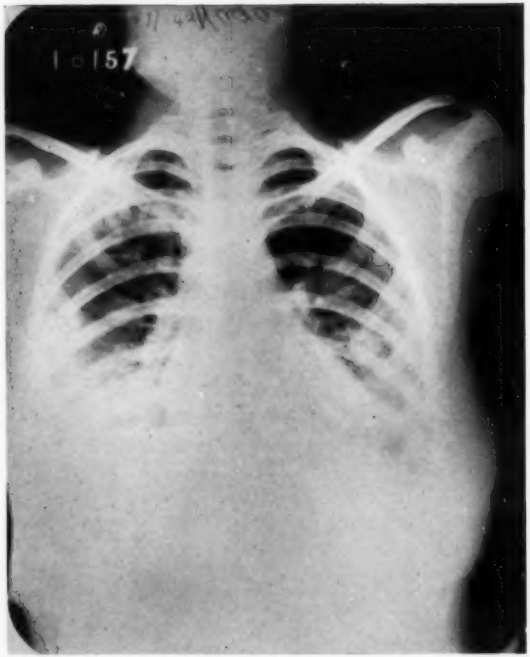

FIG. 3

Radiograph of chest (10th January, 1957) showing number of round opacities in left chest. Further round opacities are present in right lung-field and some areas of lobular consolidation.

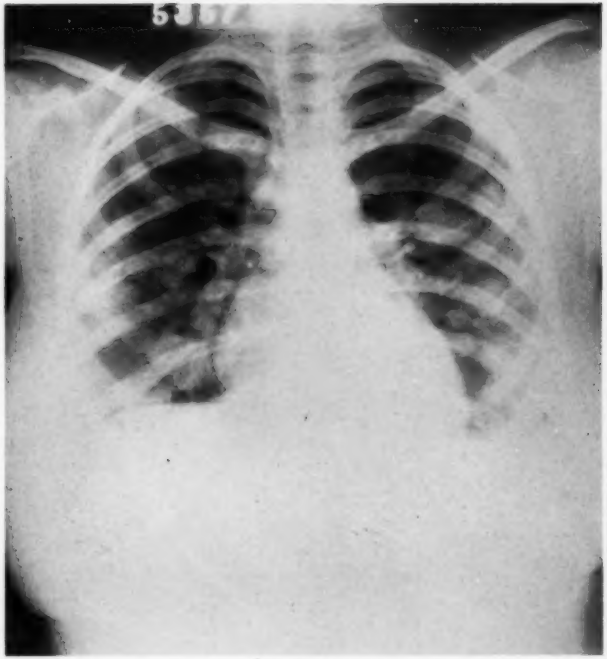

FIG. 4

Further chest radiograph (4th March, 1957) prior to surgery shows progression of metastatic lesions in both lung-fields.

FIGS. 5a and 5b

Early and late arterial phases of aortogram showing vascular mass in pelvis. There is evidence of arteriovenous shunts.

A.M.R., M.H.W., W.J.W.

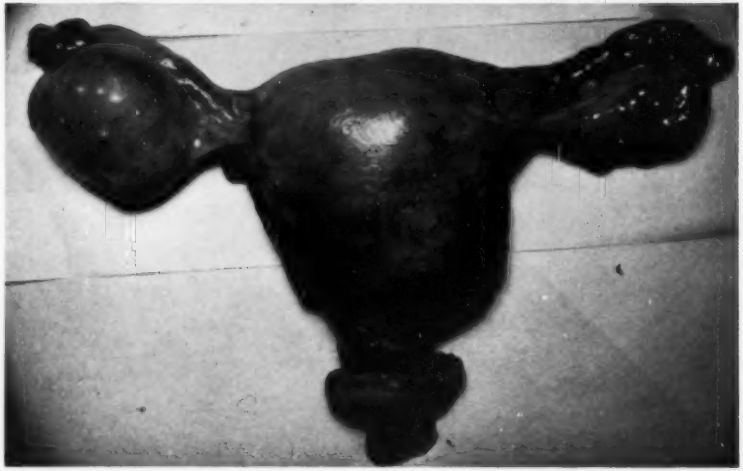

FIG. 6

Photograph of the operation specimen which demonstrates the slightly enlarged cystic ovaries and the tumour mass on the right side of the body of the uterus anteriorly. Uterus is slightly enlarged.

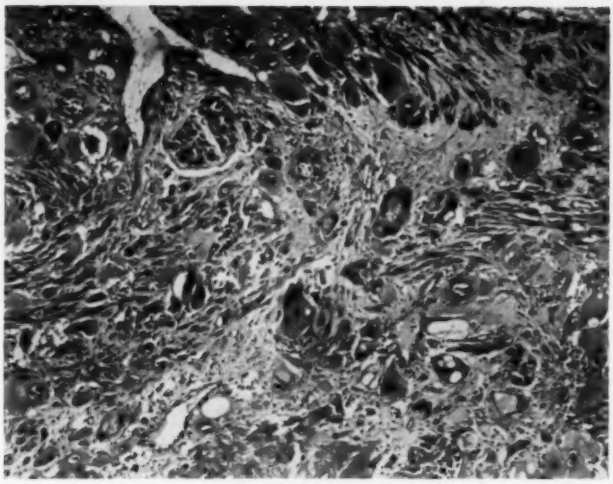

FIG. 7

Photomicrograph of the small haemorrhagic lesion of anterior wall of uterus, showing invasion of the uterine wall by tumour. ×320.

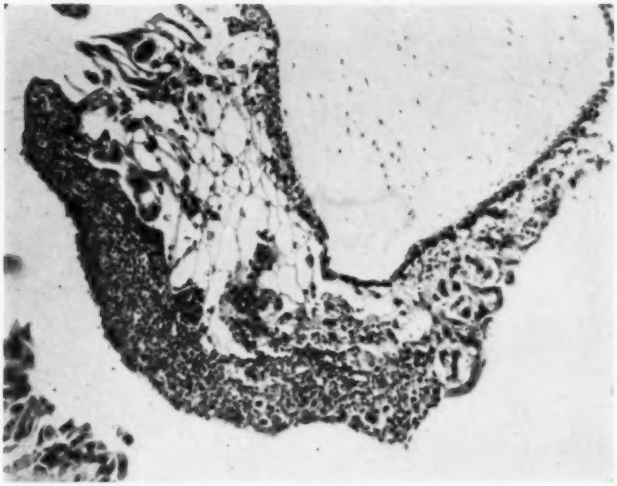

FIG. 8

Villous pattern demonstrated in section from operation specimen. ×80.

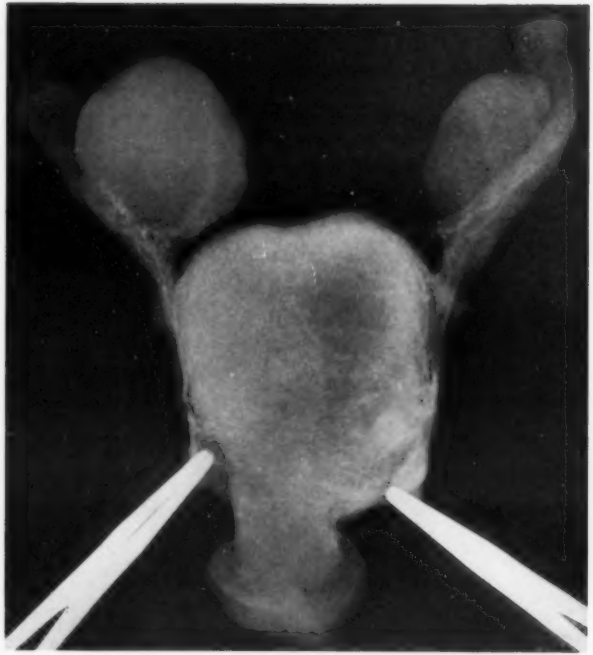

FIG. 9

Radiograph of the operation specimen following the injection of the uterine arteries with 50 per cent diodone. The vascularity of the tumour, uterus, ovaries and tubes is well demonstrated.

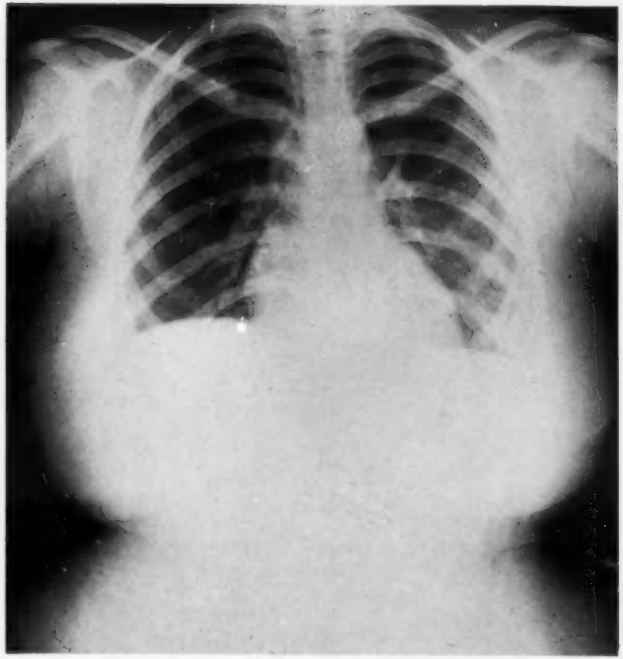

FIG. 10

No evidence of secondary deposits detected in chest radiograph taken in May, 1958.

trophoblast is going to do. The fate of the trophoblastic proliferation does not depend so much on the trophoblastic cells which are normally invasive as on the reaction of the maternal organism; and this reaction cannot be measured.

Against this the excretion of the gonadotrophic hormone can be measured and is a guide to treatment in an individual case. Unfortunately the gonadotrophic titre is of no help in separating the benign from the malignant lesion. Hobson (1958) states that negative biological tests are to be expected within 4 weeks after complete removal of the retained chorionic tissue. Should it still be positive after this stage, then there are 4 possible explanations:

(*a*) Residual trophoblastic tissue is present;

(*b*) Enlarged cystic ovaries may be acting as reservoirs for the hormones;

(*c*) Chorionepithelioma or chorioadenoma has developed;

(*d*) The patient is again pregnant.

If the biological test remains positive, especially if the titre is rising, is total hysterectomy with bilateral salpingo-oöphorectomy indicated?

Transfer of trophoblastic tissue to the lungs can occur in normal pregnancy and can be regarded as physiological metastasis. A review of a maternal death due to pulmonary emboli of the trophoblastic cells from a hydatidiform mole was well documented by Trotter and Tieche (1956). Gérin-Lajoie (1954), reporting a case of chorionepithelioma of the lung, could not eliminate the possibility of a chorionepithelioma developing in a previously benign trophoblastic metastasis. It is to be remembered that invasion of the maternal blood sinuses occurs normally and is more likely with trauma. The trauma occurring during expulsion of the mole, or at curettage, could give rise to metastatic deposits, especially in the lung. In our case, the progress from a clear chest to the stage of multiple lesions threatening cor pulmonale through to gradual resolution, has been recorded.

Serial radiography of the patient's chest is an integral part of the follow-up programme in both moles and chorionepithelioma. It is difficult to assess the place of aortography in the investigation of cases of moles and chorionepithelioma. According to Borell and Fernström (1958) contrast filled veins are noted early in the arterial phase in chorionepithelioma and mole. Also venous filling late in the arterial phase is seen with miscarriage, missed abortion and ectopic pregnancy.

At this stage it would seem of value to continue with aortography in the investigation of these cases, as the reports of Borell and Fernström are the only ones available in the current literature. It is of interest to note that our findings agree with these authors.

The clinician, faced with the problem of a patient with a hydatidiform mole who continues to show chorionic activity after removal of the mole, has a serious responsibility. In most cases he cannot expect guidance from the pathologist till after he has made his decision to remove the womb. Novak recognized this and admitted that many uteri would be sacrificed in order to save a few, and held that this was justifiable. Chorio-gonadotrophic estimations can be regarded as confirmatory evidence only. At present dilution tests as a means of distinguishing between grades of malignancy, are of little value. Radiology does not differentiate between stages of malignancy.

In the final rendering the clinician, with the knowledge that if he waits too long he may be too late, has to make his decision on clinical grounds. If the patient approaches 40 he can comfort himself that he is taking prophylactic action. In a younger woman, the decision is of a much more responsible nature.

Conclusion

The diagnosis of trophoblastic tumours of the uterus is fraught with difficulty. The histological appearance of curetted fragments is usually not conclusive. Radiological confirmation of distant spread to the lungs is not diagnostic of chorionepithelioma by virtue of the fact that blood vessel invasion by trophoblast is physiological and spread to the lungs is purely mechanical transportation. In the case just described, although there was not complete unanimity among histopathologists, the majority opinion was for chorioadenoma destruens. This diagnosis supports the contention of Novak and

Seah (1954) that recognizable villi are rarely seen in chorionepithelioma. Despite the relatively benign nature of the tumour, however, it was all too apparent to those responsible for the patient's welfare that the continual replacement of pulmonary alveolar tissue by tumour could have only one outcome. The prompt resolution of the chest lesions following pelvic clearance justified such a drastic step in a young patient. Whatever the diagnosis it seems then that the surgical treatment for chorioadenoma destruens with metastases is the same as for chorionepithelioma.

Hormonal studies in the present case gave no information not already available from radiological studies.

Summary

A case of chorioadenoma destruens has been reported in a 16-year-old unmarried girl, treated with multiple transfusions, manual removal of molar tissue and then two subsequent curettings. A total hysterectomy with bilateral salpingo-oöphorectomy was performed and 2½ years later the patient was fit and well.

Serial aortography was carried out as part of the clinical investigations in this patient. It is the first case of chorioadenoma destruens in which this examination has been performed, and arteriovenous shunts were demonstrated in the early and late arterial phases. The place of aortography has not been determined and must await further experience in this field.

The operation specimen and the histological slides were reviewed by the Chairman and Members of the Albert Mathieu Chorionepithelioma Registry (C.R.507). That this service is available to all clinicians deserves fuller recognition by those dealing with this group of diseases.

Acknowledgments

Dr. A. C. H. Wilkinson was responsible for the photographs of the pathological specimens. Mr. R. B. Sparke prepared the photomicrographs and copies of the radiographs. Mr. B. H. Curtis and Miss E. Wallace are to be thanked for their care and help in the production of the radiographs. Dr. Edmund R. Novak initially reviewed the histology in this case and very kindly arranged for all the material to be seen by the members of the Chorionepithelioma Registry. Dr. John I. Brewer, Chairman of the Albert Mathieu Chorionepithelioma Registry, presented the findings of the Committee. We thank them for their co-operation and acknowledge their help.

Dr. H. F. Bettinger, Director of the Department of Pathology, the Royal Women's Hospital, Melbourne, is to be thanked for his personal communication.

The Tasman Vaccine Laboratory Limited carried out the routine Friedman tests, as well as the quantitative examinations.

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A NEW TECHNIQUE FOR CORRECTION OF RETROVERSION-FLEXION OF THE UTERUS BY THE VAGINAL ROUTE

BY

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IN modern gynaecological practice, correction of the retroverted-flexed uterus is but seldom indicated. In retroversion associated with pelvic endometriosis, inflammatory adnexal disease, fibromyomata, etc., operative treatment is directed to the pelvic pathology present and correction of the abnormal position of the uterus is an incidental step of the surgical procedure. Mobile retroversion with no associated pelvic pathology, as a rule, gives rise to no symptoms; any complaint present in such cases is more often than not explainable by some other cause.

It is nevertheless true that some parous women with a mobile retroverted uterus, who have no other pelvic abnormality apart from the uterus being perhaps bulky and subinvoluted, occasionally complain of such symptoms as congestive dysmenorrhoea, menorrhagia, backache or dyspareunia which, after thorough and conscientious examination, can safely be attributed to the uterine malposition. Correction of the latter in such exceptional cases is usually followed by dramatic relief of the patient's complaints. The same applies, although even more rarely, to certain cases of secondary sterility and of secondary habitual abortion.

When correction of the mobile retroverted uterus is indicated, the gynaecologist has to choose between subjecting his patient to an abdominal operation and condemning her to a pessary life. A pessary often fails to maintain the uterus in correct position and, if not meticulously cared for, its use may be complicated by vaginal inflammation, discharge and ulceration. But it is chiefly on account of the psychological and physical discomfort entailed by its constant use that, in the author's opinion, a pessary should only, if at all, be used as a pre-operative measure to test the effect on the patient's symptoms of maintaining the uterus in the anteverted position.

Numerous abdominal procedures for the correction of retro-displacement of the uterus have been devised. Of these, the various modifications of the Gilliam (1900) operation (transplantation of the round ligaments into the abdominal wall) are the most effective and the most widely practised. We have had considerable experience with modified Gilliam techniques. The results are usually satisfactory but three disadvantages of the operation may be mentioned: (1) It entails opening the abdominal cavity and to this not a few patients object. (2) The anterior suspension of the uterus often becomes less satisfactory with the lapse of time and particularly following pregnancy and labour. Some time after the operation the uterus is frequently found to occupy a position midway between anteversion and retroversion. (3) Pain and tenderness at the points of fixation of the round ligaments to the abdominal wall are very commonly complained of.

In recent years, little attention has been given to vaginal operations for the correction of retroversion except when the latter is associated with

prolapse. Such operations were mainly based on two principles: either fixation of the cervix to the posterior vaginal fornix or fixation of the body of the uterus to the anterior vaginal wall. The former procedure is anatomically unsound and is almost invariably followed by recurrence of the malposition. The latter not only interferes with bladder function but is also not consistent with the growth of the uterus in pregnancy and is therefore unsuitable for women in the child-bearing period. It is not therefore surprising that the use of such operations has long since been discontinued.

A technique of vaginal correction based on an entirely different principle was devised by Wertheim. Originally, he delivered the uterus through a transverse vaginal incision and sutured the two round ligaments to each other. When the uterus was bulky, he sometimes concluded the operation by fixing the round ligament end to the angle of the transverse incision. Being not satisfied with the results of this technique, Wertheim subsequently modified it and his modified operation was practised and described by Werner and Sederl (1952). In this, the round ligaments are pulled out through holes made in the vaginal wall on either side and are fixed therein by means of silk sutures.

This technique was given a trial in our clinic and we were impressed with its simplicity and its success in satisfactorily correcting the uterine malposition. But the holes made in the vaginal wall and the loops of round ligaments left in the vaginal cavity almost always gave rise to trouble. These usually became septic sooner or later and sometimes sloughed away. Persistent offensive discharge was a common complication. Most patients were conscious of the presence of abnormal "nodules" in the vagina and some complained of dyspareunia which was not present before operation. These undesirable sequelae seem to be the reason why this simple and otherwise satisfactory technique has enjoyed little popularity.

We thought of a simple modification which made it possible to shorten effectively and fix the round ligaments to the vaginal wall without pulling loops of these ligaments into the vaginal cavity. This modified procedure has given us excellent results.

Operative Technique

(1) The vagina and cervix are painted with a suitable disinfectant. The bladder is evacuated by a metal catheter.

(2) The posterior vaginal wall is retracted by a posterior speculum, the cervix is exposed and its anterior lip is grasped with a volsellum.

(3) Strong downward and backward traction is applied to the cervix and the bladder is retracted upwards by means of a suitable anterior vaginal retractor.

(4) A midline incision is made in the anterior vaginal wall extending from a point 3 cm. below the external urethral meatus to the point where the vaginal mucosa is reflected on to the cervix (Fig. 1).

(5) Curved bladder forceps are applied to the edges of the incision and the bladder is dissected laterally from the anterior vaginal wall first on the right and then on the left side keeping the vesico-vaginal fascia on the bladder side.

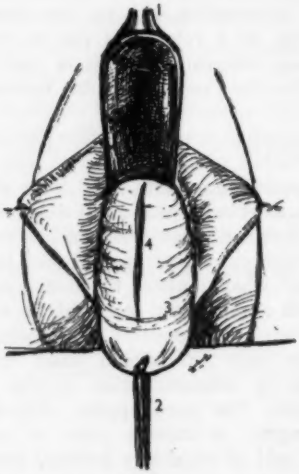

Fig. 1

Midline incision in anterior vaginal wall (diagrammatic). 1. Anterior vaginal retractor pushing up the bladder. 2. Cervix pulled downwards by volsellum (degree of cervical descent exaggerated). 3. Line of reflection of vaginal mucosa on to cervix. 4. Longitudinal midline incision in anterior vaginal wall.

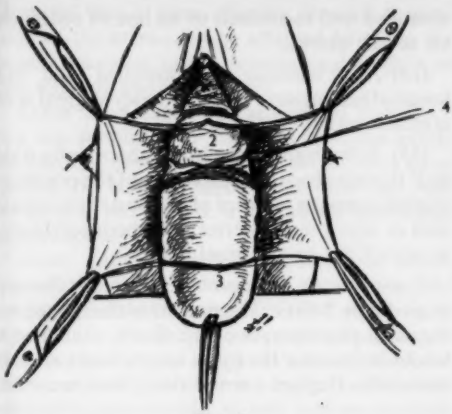

FIG. 2

Vesico-uterine peritoneum opened (diagrammatic). 1. Vaginal wall reflected laterally. 2. Bladder displaced upwards. 3. Cervix. 4. Suture on anterior edge of divided peritoneum.

(6) The vesico-cervical ligament is divided by a suitably curved scissors and the bladder is dissected upwards until the vesico-uterine peritoneum is exposed. The peritoneum is opened and a fine catgut suture is applied to its anterior edge to serve as a landmark at a later stage of the operation (Fig. 2).

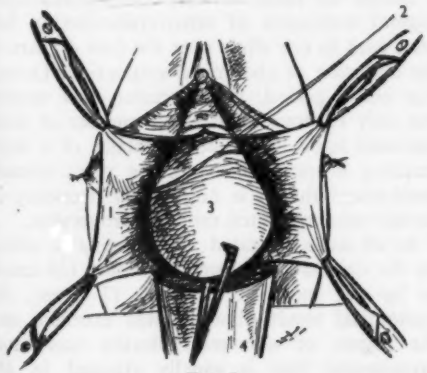

FIG. 3

Body of the uterus delivered into the wound (diagrammatic). 1. Vaginal wall reflected laterally. 2. Suture on anterior edge of divided peritoneum. 3. Body of uterus. 4. Posterior speculum.

(7) With the help of both index fingers and a fine one-toothed volsellum the body of the uterus is delivered into the wound (Fig. 3). This is made easier by the assistant pushing the cervix upwards and backwards into the posterior fornix. Any bleeding from the body of the uterus caused by the volsellum is controlled with No. 00 catgut sutures.

(8) The assistant pulls the uterus downwards and to the left. The right round ligament is identified and is grasped with a long Spencer Wells artery forceps at a point about 2·5 cm. from the uterus. By pulling on the forceps in a downward and medial direction a loop of the round ligament is formed (Fig. 4). A thick nylon suture is passed so as to include both limbs of the round ligament loop just proximal to the Spencer Wells forceps and is tied. Both ends of the suture are left long and a needle is threaded to each end.

(9) Traction is applied to the bladder forceps holding the edge of the vaginal wall and the two ends of the nylon suture are passed through the vaginal wall from within outwards so as to emerge about 1·5 cm. apart at a point about 2 cm. from the vaginal edge and nearer to the

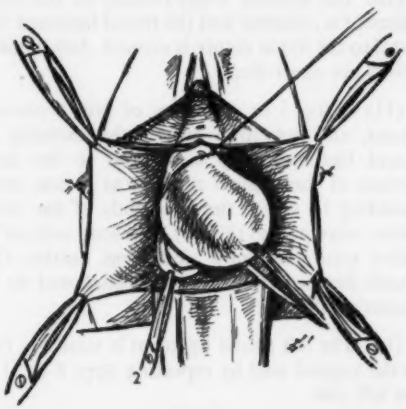

FIG. 4

Round ligament grasped with Spencer Wells forceps (diagrammatic). 1. Body of uterus pulled downwards and to the left. 2. Spencer Wells forceps on right round ligament.

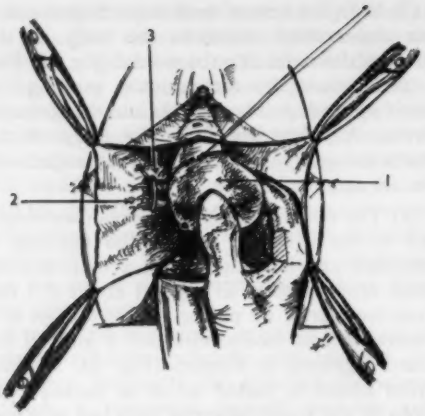

FIG. 5

Round ligament anchored to vaginal wall (diagrammatic). 1. Body of uterus pulled downwards and to the left. 2. Catgut sutures fixing round ligament raw area to vaginal wall. 3. Nylon suture on round ligament.

urethral meatus than to the cervix. The two ends of the nylon suture are left long but are not tied at this stage.

(10) The Spencer Wells forceps on the round ligament is removed and the round ligament loop distal to the nylon suture is excised. Any bleeding points are controlled.

(11) Using 3 or 4 sutures of No. 1 chromic catgut, the raw area created by excising the round ligament loop is sutured to the inner surface of the vaginal mucosa at a site corresponding to where the long ends of the nylon suture were passed (Fig. 5). The long ends of the nylon suture are now tied from outside. The round ligament is thus firmly anchored to the vaginal wall.

(12) The left round ligament is similarly fixed to the vaginal wall by repeating steps 8 to 11 on the left side.

(13) The body of the uterus is now replaced inside the peritoneal cavity. By applying traction to the fine catgut suture marking the edge of the divided peritoneum the latter can be easily identified and re-sutured to its line of reflection on to the uterus.

(14) Any bleeding is controlled and the longitudinal incision in the anterior vaginal wall is closed without drainage.

(15) If the vaginal introitus is abnormally wide or if there is abnormal relaxation of the posterior vaginal supports, descent of the posterior vaginal wall or rectocele, posterior colpoperineorrhaphy is carried out on the usual lines.

Post-operative Management. Antibiotic therapy is given for 5 days. The patient is discharged on the sixth post-operative day. She is examined 6 weeks later and if the nylon suture knots are still discernible they are cut and the sutures removed.

DISCUSSION

Vaginal correction should not be attempted in cases of fixed retroversion or in cases of retroversion associated with pelvic pathology. It is also unsuitable for nulliparous women for it is difficult to gain satisfactory access to the round ligaments through a narrow vagina. Many of these latter patients have a hypoplastic uterus for which retroversion seems to be the natural inclination. It is therefore doubtful if it is ever wise to try to antevert the retrodisplaced nulliparous uterus by any method.

Except for these obvious contra-indications, vaginal correction of retroversion-flexion has been used in our clinic over the past 4 years to the exclusion of abdominal suspension. During this entire period, the operation was carried out only 17 times. This small number of cases operated upon in the busy practice of a large teaching hospital illustrates the point already emphasized that it is only rarely necessary to correct uncomplicated mobile retroversion.

In all cases operated upon vaginally, either by the original Wertheim procedure (10 cases) or by our modified technique (7 cases), the anatomical result obtained was excellent and the degree of anteversion-flexion was more pronounced than is usually attained by abdominal suspension. In all cases followed up, the corrected position of the uterus was maintained and in no case was this affected by pregnancy or parturition. It can hardly be

disputed that a more effective forward suspension of the uterus can be attained by fixing the round ligaments to the anterior vaginal than to the anterior abdominal wall.

Other advantages of the vaginal procedure are the simplicity of the technique, the extraordinarily smooth convalescence, the short period of hospitalization and, last but not least, that the patient is spared an abdominal intervention.

Apart from the inconveniences and minor complaints above described to follow the original Wertheim procedure, and which were obviated by the use of our modified technique, no complications of any kind were encountered with vaginal correction. Indeed, the new operation is so simple, so safe and so anatomically effective that its major drawback seems to be the risk of its indiscriminate application to cases of retrodisplacement with no definite indication for correction.

Summary

A new technique for correcting mobile retroversion-flexion of the uterus by vaginal operation is described. It is applicable to parous women with no associated pelvic pathology. Correction of this type of retroversion is but seldom indicated. When it is, the technique described is in many ways superior to abdominal suspension. Vaginal correction is a simple and safe procedure which can be carried out if necessary on patients considered as poor surgical risks. There is no place in modern gynaecology for condemning a woman to a pessary life.

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OBSTETRICS IN THE BIBLE

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"Be fruitful, and multiply." (Gen. i. 28.)

THIS was the first commandment given by God to man. As a result thereof, a goodly portion of the Bible concerns itself with reproduction, and by collecting and correlating these allusions to pregnancy and parturition, we can gain a fairly coherent view of the theory and practice of obstetrics in the biblical area during the biblical era. Occasionally it is necessary to note the beliefs and customs of other ancient nearby civilizations in order to throw light on biblical obscurity.

It is also necessary to note that the writing of the Old Testament was begun during the golden age of religious creativity, *circa* 700 B.C.—a period that saw the rise of the major Hebrew prophets, the influence of Zoroaster, and the beginnings of Buddhism. Old Testament writing continued until about 200 B.C. and, from about that time until perhaps a century after Christ, most of the Apocrypha was penned, while the New Testament was written from about A.D. 50–150. Thus this period of about 800 years chronicles the views and practices of obstetrics as recounted in this body of sacred writing.

PREGNANCY

It is of fundamental importance to appreciate the pressing necessity for male offspring among the biblical Hebrews. While the reasons for this would divert our interest into fields not immediately relevant to the subject—such as views on the after-life and the levirate marriage—it must be understood that in the whole of the Old Testament there is no greater curse than Jeremiah's "Write ye this man childless"! (xxii. 30). The alleged 1,000 wives of Solomon (1 Kings xiii. 11) did not exist solely to multiply his pleasures, but to multiply his progeny. Jeroboam had 88 children, born of but 78 wives (2 Chron. xi. 21)—a shameful waste of fertile womanhood.

Daughters had a lowly status in the ancient Near East. While the Hebrews did not subscribe to the extreme views of an early Persian writer that "Men do not pray for daughters, and angels do not reckon them among their gifts to mankind" (Durant, 1954), yet the birth of a daughter was not an occasion for rejoicing. The gospel of John attributes to Jesus the remark that "A woman when she is in travail hath sorrow . . . but, as soon as she is delivered of the child, she remembereth no more the anguish, for joy that a man child is born into the world" (xvi. 21). Not just any child—specifically a "man child". The function of daughters was but that they should in turn become the mothers of sons. So important was pregnancy, that Judges v. 30 actually designates a woman as "a womb". The English translation of this passage uses the term "damsel", but the Hebrew word is "raḥam" which means "womb".

Since childbearing was of such paramount importance, the fertile woman was honoured, while the barren was pitied. When Hagar knew that she was with child, she could afford to become insolent to her mistress Sarah (Gen. xvi. 4). The occurrence of a pregnancy took away Elizabeth's reproach (Luke i. 25). Tamar, a widow, and the two daughters of Lot resorted to incest in order to become pregnant (Gen. xxxviii. 18 and xix. 36), while Rachel cried to her husband Jacob "Give me children or else I die"! (Gen. xxx. 1). However, despite this single-mindedness of purpose grand multiparity was uncommon. The largest number of pregnancies in women apparently did not exceed seven (1 Sam. ii. 5; Jer. xv. 9).

Understandably enough, the Bible considers that pregnancy is not a fortuitous occurrence, but a precious gift bestowed by God. Thus Jacob's rejoinder to Rachel's plea was "Am I in God's stead, who hath withheld from thee the fruit of the womb?" (Gen. xxx. 2). We read that God granted conception to Ruth (iv. 13), to Hannah (1 Sam. ii. 21), to Manoah's wife (Judges xiii. 3), and to Eve, who, on bearing Cain, exclaimed "I have gotten a man from the Lord" (Gen. iv. 1). The author of Psalm xxii. 9, 10 claims: ". . . thou art he that took me out of the womb: . . . thou art my God from my mother's belly."

God likewise was instrumental in causing sterility. He closed the wombs of Sarah (Gen. xvi. 2), Hannah (1 Sam. i. 6), Michal (2 Sam. vi. 23) and of the women in Abimelech's household (Gen. xx. 18), while he opened up the wombs of Leah (Gen. xxix. 31) and Rachel (Gen. xxx. 22). He also permitted post-menopausal conception in an incredulous Sarah (Gen. xviii. 10–12) and in Elizabeth (Luke i. 36). We can thus readily understand that the treatment of sterility was prayer. Thus Hannah beseeched God for "a man child" (1 Sam. i. 11) while "Isaac intreated the Lord for his wife, because she was barren . . . " (Gen. xxv. 21).

It must not be imagined, however, that the biblical matriarchs were content with prayer. They did employ other means as well in order to promote pregnancy. Though the biblical editors have been assiduous in expurgating all ungodly references to wizardry, divination, charms and incantations, yet a number of references are revealing in this regard. For example, there is the curious story of the mandrakes related in Gen. xxx. 14. We read that Rachel bargained for, and acquired some mandrakes from her sister Leah. And there the story suddenly ends. We don't know what happened as a result of her getting this plant, or why she wanted it in the first place. Now early beliefs have credited the mandrake (mandragora) with aphrodisiac and fructifying powers, so that presumably Rachel wanted them for the latter purpose, and that in the original version of the story she in fact conceived with their aid; but the biblical editors, sensing the idolatrous nature of such a tale, broke it off short and substituted a more seemly phrase: "God opened her womb" (Gen. xxx. 22) (Gore *et al.*, 1928).

Then there are references to "teraphim" (a plural noun) (Gen. xxxi. 19, xxxi. 30), i.e., images, household gods, treasured by Rachel. These were "in all probability amulets . . . figurines . . . associated with the cult of the mother goddess, and used as charms to secure the increase of man" (Gore *et al.*, 1928). Understandably enough, Michal, who remained sterile all her life, possessed an image (1 Sam. xix. 13).

Finally one must observe two female divinities who figure in the Bible, "Ashtoreth" (Judges ii, 13, x. 6; 1 Kings xi. 5) (the Babylonian "Ishtar") was a local goddess of fertility, and possibly also exercising this function was "Asherah", originally a female divinity, and falsely translated as "groves" in the Authorized version (Deut. vii. 5, xii. 3, xvi. 21; Judges vi. 25).

Impregnation

The Bible illustrates some novel and interesting views on the matter of impregnation. Pregnancy was considered to follow on the deposition of semen in the suitable nidus of a womb. There was of course no conception of sperm, or of ovum. Any man who was capable of producing semen was *ipso facto* capable of producing offspring, provided the womb receiving the semen was "open". Thus the Bible understands only female sterility. Despite God's curse on Abimelech "Behold thou art but a dead man" (Gen. xx. 3), i.e., a man whose seed would not be fruitful, there is really no conception of male sterility. The womb was looked on simply as an incubator to house the semen which would eventually develop into a child.

While the Bible sheds no light on the male "seed", both the Talmud and the Koran mention that the semen originated in the head and reached the genitals via the spinal column (Gordon, 1955). Presumably the biblical Hebrews entertained similar misconceptions.

The fructification of seed within the womb is noted thus: "My substance was not hid from thee, when I was made in secret . . . My undeveloped substance ('golem'—Hebrew) did thine eyes see . . . " (Psalm cxxxix. 15, 16). The "golem" is the earliest stage of the embryo.

The inference may be drawn that the Bible does not consider physical cohabitation to be an absolute prerequisite for pregnancy. It is possible that the tale of the pregnancy of Lot's daughters (Gen. xix. 31–38) indicates their artificial insemination by their father's emission—produced by stimulation during a drunken stupor (Brim, 1936). It is also believed of ben Sira (*c.* 180 B.C.), writer of the apocryphal Ecclesiasticus, that he was born after accidental insemination. His mother entered a bath shortly after it had been vacated by her own father, and there received her father's seed. She thus became pregnant, and called her son ben Zera (son of Seed), but when the lad grew up and realized the significance of his name, he was ashamed, and changed it to ben Sira (Trachtenberg, 1939).

Conceptions without human masculine intervention were not too unusual in antiquity. Jesus was so conceived (Matt. i. 18), and so were Buddha, Zoroaster (Durant, 1954), many of the pharaohs, Julius Caesar, Augustus, Alexander the Great, Cyrus, and many lesser lights (Smith, 1953). Here in South Africa we have the instance of the Hottentot deity—name of Heitsi Kabib—being born of a woman following on the sexual intervention of the stars.

The Bible also illustrates an obscure parallel between the process of breathing and the production of semen. According to a late legend (never embodied in the gospels or in ecclesiastical doctrine), Jesus was conceived following Mary's impregnation by the breath of the Holy Ghost in her ear—a legend which is frequently illustrated by medieval artists and which has parallels in early Mongolian, Persian, Indian and Egyptian writings (Smith, 1953; Stevenson and Guthrie, 1944). The bald remark of Gen. ii. 7 that the Lord breathed into Adam's nostrils the breath of life, thus becomes pregnant with sexual significance, as does the remark of the apocryphal mother in 2 Macc. vii. 21–22: "'Twas not I who gave you the breath of life . . . 'Twas the creator of the world . . . " Well known in Egyptian mythology is the account of the birth of Queen Hatshepsut, a rather remarkable woman of the 18th dynasty. The offspring of Thothmes I and his sister Aahmes (brother-sister unions were the rule among Egyptian nobility), she nevertheless had herself depicted as being born of her mother Aahmes and the god Amen-Ra, who is indicated as holding the Symbol of Life (☥) to the nostrils of Aahmes, thus impregnating her. Here breath becomes synonymous with semen, and respiration with sexual intercourse (Margetts, 1951).

Antenatal Care

We may possibly draw the inference that pregnant women shied away from exposing themselves to dangerous and unpleasant influences, as these might conceivably adversely affect the unborn infant. The tale of Jacob and the speckled sheep (Gen. xxx. 39) illustrates this belief in maternal impression.

Dietary advice is offered by an angel to the wife of Manoah, shortly to be with child. "Now therefore beware . . . and drink not wine nor strong drink, and eat not any unclean thing" (Judges xiii. 3–4).

Prenatal examination of Rebekah by God, to whom she had actually gone for antenatal advice (Gen. xxv. 22), indicated the presence of twins: "Two nations are in thy womb . . . " she was told (Gen. xxv. 23), a diagnosis fully corroborated, for "And when her days to be delivered were fulfilled, behold, there were twins in her womb" (Gen. xxv. 24). A similar diagnosis was made by a midwife in the case of Tamar. This midwife was so certain of the presence of twins that she had made ready a scarlet thread to tie round a presenting hand (Gen. xxxviii. 28) in order to establish primogeniture.

Important factors in the preparation for childbirth were the measures taken to deal with the multitude of demons and evil spirits who were wont to produce a miscarriage or else to inflict disease or death on the newborn. A number of Mesopotamian demons specialized in the neonatal field. Pre-eminent among them was Lilith, an Assyrian demon who had to be propitiated and kept away by means of charms and incantations. She is specifically mentioned by Isaiah xxxiv. 14 as a "night monster" (also translated as "screech owl"; Hebrew term is Lilith) and is thought to be referred to as well (but this is very probably a misconception) as "the terror by night" of Psalm xci. 5. It is conceivable that the very term "lullaby" (lili aby) is

really an incantation against Lilith (Smith, 1953). Zoroaster, at his birth, laughed aloud, so that the demons clustered about him fled in tumult and terror (Durant, 1954).

A semantic exercise will permit us to hazard that drugs were previously made ready to ease the pains of labour. The story of the mandrakes (mandragora) in Gen. xxx. lends itself to alternative explanations. While Egyptian beliefs credited the mandrake with aphrodisiac properties, Babylonian opinions indicated that its primary function was that of a soporific and anodyne, and this is the concept that has generally prevailed:

"Not poppy, nor mandragora,
Nor all the drowsy syrups of the world,
Shall ever medicine thee to that sweet sleep
Which thou owedst yesterday"
(*Othello*, III, iii, 334).

So it seems reasonable to suppose that Rachel, only a generation removed from Babylonia, would have shared Babylonian beliefs on the function of the mandrake. Perhaps then, at the time that she bargained with Leah, she was already pregnant, and wanted the mandrake to ease the expected pangs of a first labour (Thompson, 1934).

Normal Labour

The pain associated with childbirth is referred to several times in the scriptures (1 Sam. iv. 19; Gen. xxxviii. 27; Jer. xlviii. 41, xlix. 22; John xvi. 21). Jeremiah seems to have evinced considerable interest in medicine. A number of his remarks reveal him to be an astute clinical observer. At any rate he notes that labour is more painful in a primipara: "For I have heard a voice as of a woman in travail, and the anguish as of her that bringeth forth her first child" (Jer. iv. 31). It should be noted that the punishment for Eve, as given in Gen. iii. 16 is "In sorrow shalt thou bear children". While there is a general impression that this punishment meant that parturition was henceforth to be associated with pain, it must be pointed out that the Hebrew word used in this sentence ("etsev") does not indicate pain, but sorrow or sadness. Does this punishment in fact have bearing on puerperal depression rather than pain?

Marriage in ancient Israel took place at an early age and motherhood occurred shortly after puberty. Parturition was a hazardous matter: "The ways of entering this world were made narrow, grievous and toilsome . . . full of dangers and burdened with great hardships" (2 Esdras vii. 11–12). "Thou shalt honour thy mother all the days of her life: for thou must be mindful of the great perils she suffered for thee in her womb" (Tobias, iv. 4). Delivery took place in the home, although there is also reference to parturition in the fields (Cant. viii. 5) a procedure surely carrying a lesser risk of sepsis. Delivery outside the tent is still often the case among the present-day Beduin (van Selms, personal communication). Affluent Egyptian women had access to special lying-in homes.

Delivery was usually effected by means of friends (Ruth iv. 13; 1 Sam. iv. 20) and relatives, probably women who themselves had experienced numerous pregnancies. Professional midwives also existed (Exod. i. 15; Gen. xxxv. 17, xxxviii. 28), and, understandably enough, a grateful mother commonly expressed thanks to God for a successful birth (Ps. xxii. 9–10) in much the same manner as today, when a grateful father will insert an advertisement in the paper thanking God as well as the doctor and staff.

Reference to Egyptian hieroglyphics indicates that cephalic presentation was the rule. The hieroglyph for "to give birth to" is a picture of a squatting woman with the foetal head emerging from the perineum (Sigerist, 1951).

A set formula is used in the scriptures to indicate labour after a full-term gestation: "And when her days to be delivered were fulfilled . . ." (Gen. xxv. 24). "Now Elizabeth's full time came that she should be delivered" (Luke i. 57), "and so it was that . . . the days were accomplished that she should be delivered . . . " (Luke ii. 5–7). Exod. i. 19 refers shortly to rapid easy labour. A note on the parturition of Tamar (xxxviii. 29) suggests that she had an unusually roomy pelvis, since the twins within her could move so easily. On the other hand her perineum might have been torn by the exit of the first twin for she called his name Pharez—which means "to burst", "to break out". Perhaps he emerged in precipitate haste, or perchance it was the perineum that was torn; possibly both.

Labour took place with the woman in the squatting position. In Egypt, at any rate, the parturient woman had two helpers—one supporting her from behind, while the other crawled underneath her, ready to receive the infant (Dawson, 1929). Significantly, two midwives are mentioned in Exodus i. 15. The baby was thus delivered on to the lap of the crouching assistant. Interestingly enough, Rachel said to her husband: "Behold my maid Bilhah, go in unto her; and she shall bear upon my knees" (Gen. xxx. 3). A number of children were also brought up on Joseph's knees (Gen. i. 23). Was he in fact assisting the accoucheur? The possibility is not so remote as might appear. Statuettes from places as far removed as Cyprus and Peru indicate an interesting method of delivery which might have had parallels to the Egyptian and Hebrew methods of parturition. The statuettes indicate the parturient woman actually sitting on the lap of an assistant—perhaps even her husband—who supports her trunk from behind, while another helper receives the infant. This would make the remark about Joseph's knees more intelligible. Job refers to being born on the knees (iii. 12). In the case of the birth of Jesus it is mooted that the three male priests (magi) actually rendered obstetric assistance (Elgood, 1934), an unlikely possibility since they only started out from their journey at the moment of birth. The assumption that there were three priests is pure legend—derived from the fact that there were three gifts.

The Bible also deals with an alternative method of delivery, yet one which may be derived originally from the woman sitting on the lap of an assistant. The birth-stool or obstetric chair is still in use today in backward districts of the Arab countries. "It was not until the 19th century that the obstetric chair ceased to be a necessary equipment of the midwife. Mauriceau of France in the 17th century was the first to use a bed for childbirth" (Haggard, 1929). Exod. i. 16 refers to "ovnaim", rendered "stools" in English. In Hebrew the term is not singular, nor plural, but is a dual number, so that "ovnaim" refers to "two stones", and reference to Jer. xviii. 3 suggests that they were constructed of clay. When the Egyptian language dropped its dual form *c.* 1300 B.C. (Yahudah, 1947), it was called "the brick" (of bearing), and this coincided with the introduction of an additional brick to unite the two structures—so that instead of two parallel bricks, thus, II; the addition of a posterior cross-bar united them to form a single seat, thus, U. A woman either sat on the stool itself (in the "U" type) or else sat on her haunches while her knees rested on each arm of the stool (in the "II" type stool). In either case, her trunk was supported by an assistant.

Hebrew commentators have suggested an alternative, but unlikely, meaning to Exod. i. 16. The term "ovnaim" may not refer to the obstetric chair at all, but to the testes. The passage can be read: "When ye see by the "ovnaim" (two stones, i.e., testes) that it is a boy . . . " However, the rendering of "ovnaim" as "stools" is much more satisfactory.

Regarding the third stage of labour, we have reference to the placenta (Shilya—Hebrew) in Deut. xxviii. 57. Some biblical translations render it incorrectly as "the young one". Ezek. xvi. 4 refers to cutting of the umbilical cord, which was presumably ligated thereafter. An obstetric caul (chorio-amniotic membranes) is not mentioned in the Scriptures, but was presumably recognized if we may judge by the description of the "caul of the heart" in Hosea xiii. 8.

The placenta also received some attention from the ancients. It was not an inert organ by any means. Though physically severed from the body, it nevertheless retained a spiritual affinity with the individual it had sustained within the womb. The placenta was held to house a portion of the soul and spirit of the person to whom it pulsated its life. It was a symbol for the preservation of good fortune and an amulet to ward off danger. Such conceptions were extant especially among the Egyptians, but similar views can be noted in the passage from 1 Sam. xxv. 29. Abigail tells David: "Yet a man is risen to pursue thee, and to seek thy soul; but the soul of my lord shall be bound in *the bundle of life* with the Lord thy God; and the souls of thine enemies them shall he sling out, as out of the middle of a sling." The "bundle of life" contained the preserved placenta (DeWitt, 1959).

The Egyptians believed that the placenta was the embodiment of the external soul and the

royal placenta was carried as a symbol before the pharaoh, especially on ceremonial occasions (Smith, 1953), a practice continued to the time of the Ptolemies (*c.* 325–45 B.C.). Also at least during the 4th, 5th and 6th dynasties, there existed an office known as "The Opener of the King's Placenta". "The term . . . originated from some actual or forgotten king-murder, the 'bundle of life' containing the placenta being ceremonially opened at the conclusion of the reign"—and thus the breath of life departed as well from the disintegrated contents of the bundle (Needham, 1934).

The whole of Lev. xii. is devoted to the ritual purification of a woman following childbirth. She was considered "unclean" for a week after the birth of a boy, and for two weeks after the birth of a girl. The ancients considered that the lochia lasted longer in the case of the birth of a female infant. In addition the woman was considered "unclean" (sexual relations prohibited) for a further period of 33 days after male birth and 66 days after female birth, and thereafter was ritually purified and acceptable for all activities, holy and profane.

Complicated Labour

Premature labour is referred to specifically in only one instance. At the sudden news of a personal and national catastrophe, the wife of Phineas promptly went into labour: "When she heard the tidings . . . she bowed herself and travailed . . . " (1 Sam. iv. 19).

On numerous occasions births are described without the preliminary of the set formula regarding "the days to be delivered were accomplished". The vast majority of these are brief simply because further information would be irrelevant in the context, but some considerable description is given of Tamar's pregnancy, yet when she delivered, it was but written: "And it came to pass that in the time of her travail . . . " (xxxviii. 27). Perhaps her "days to be delivered" were not in fact fulfilled and that she laboured prematurely, especially since she had twins in her womb.

Of Moses it is also written "the woman conceived, and bare a son" (Exod. ii. 2). The fact that she could safely hide him from the Egyptians for some three (lunar?) months (Exod. ii. 2) might indicate that he was, in fact, very premature. There is a legend that Reuben was premature (Ginzberg, 1956).

Markedly premature labours, giving rise to non-viable infants, that is, abortions, are not referred to specifically, but are mentioned in a number of places, among them Exod. xxi, 22, Job iii. 16, iii. 11, and 2 Esdras vi. 21. Num. xii. 12 refers to a macerated foetus in these terms: "Let her not be as one dead, of whom the flesh is half consumed when he cometh out of his mother's womb."

Postmaturity, if not mentioned in the two testaments, has at least been considered in the Apocrypha. 2 Esdras iv. 40–41 propounds a query: "Go thy way to a woman with child and ask of her when she hath fulfilled her nine months, if the womb may keep the birth any longer within her." The reply to this question is: "No . . . that it can not."

As an instance of abnormal presentation, we have the case of Tamar (Gen. xxxviii. 28) who had twins, one of which prolapsed his arm. The progress of this birth was interesting, for by some mechanism this infant withdrew his arm while the other was born—presumably by vertex; or, considering that the mother might have suffered a perineal tear, is it more likely that Pharez came breech first?

Another hand presentation occurred in the birth of Jacob, whose hand clasped Esau's heel when the latter emerged (Gen. xxv. 26).

A semantic deduction suggests that Rachel bore an infant as a breech: "And it came to pass, when she was in hard labour, that the midwife said unto her, Fear not, for this also is a son for thee. And Rachel died" (Gen. xxxv. 17–19). It appears that while the birth was still in progress, the sex of the infant had already been determined, so presumably the breech presented.

With this suggestion in view we may wonder whether Rachel died of conditions related to breech delivery—such as placenta praevia and resultant ante-partum and post-partum haemorrhage. The only other such maternal death is that of the wife of Phineas (1 Sam. iv. 20), who possibly also died of haemorrhage, although convulsions have been mooted (Mead, 1938).

The birth of twins is recorded in the case of Rebekah (Gen. xxv. 24) and Tamar (Gen. xxxviii. 27). Hebrew folklore also suggests that Eve had multiple pregnancies. Cain is thought to have been one of twins, while Abel was one of triplets. There is also a tradition that each of Jacob's sons (Joseph excepted, but including the prematurely-born Reuben) were born together with twin girls (Ginzberg, 1956). Persian legend recounts that the initial human creation was a double-sexed Siamese twin, joined together at the back. They were then divided as an afterthought. This lends an interesting basis for the echo in Gen. v. 2 telling of a similar tale: "Male and female created he them . . . and called *their* name Adam . . . " (Durant, 1954). The same idea of the first humans as being double-sexed is also found in Plato (Symposion) and in Rabbinic literature (van Selms, personal communication).

According to Luke, Mary at one stage is described as "being great with child" (ii. 5). Being a physician, may one presume that he was unduly observant and noting an instance of hydramnios? This is an unlikely possibility, for the Greek version mentions nothing about "great with child", writes only the equivalent of "pregnant".

Uterine inertia is twice referred to in identical passages: " . . . for the children are come to the birth, and there is not strength to bring forth" (2 Kings xix. 3; Isa. xxxvii. 3).

The Bible does not mention Caesarean section or the piecemeal removal of a dead foetus, although both of these are noted in the Talmud (Arakin 7; Ohalot vii. 6).

Among the ancients it was believed that coitus during the menses would result in the birth of a monster, hence the observation of 2 Esdras v. 8 that "menstruous women will bear monsters" (Crawfurd, 1916).

The Bible, dealing as it does with the most extraordinary occurrences, is somehow lacking in the reports of two conditions that one might have expected to see therein: couvade, and vagitus uterinus. To the first, the vicarious travail of a father while the wife is in labour, there is not even a remote allusion. Vagitus uterinus, the crying of an infant *in utero*, is mentioned in Babylonian writings (Ploss and Bartels, 1935). Zoroaster laughed in his mother's womb (Zimmels, 1952). Both Buddha and Jesus spoke to their mothers immediately after birth (Hannay, 1922) while ben Sira went one better; he refused his mother's milk and demanded solid food instead (Schechter, 1938). The nearest approach to this matter in the Bible is the recording of the movements *in utero* of the foetuses in the pregnancy of Rebekah (Gen. xxv. 22) and Elizabeth (Luke i. 41).

Father and Son

While it is conceivable that in certain instances the father actually assisted his wife during parturition, it is much more probable that he played a quite passive role. Jeremiah (xx. 15) makes the incisive observation that the father remained elsewhere and the news of the birth was brought to him. In Ugaritic (Phoenician) literature as well it is mentioned that a father absented himself during labour (van Selms, personal communication).

A few more remarks on the newborn are desirable. Moses, we have noted, might have been premature. This is based on the supposition that his mother laboured without there being a qualification that her "appointed time" had come; moreover, after his birth he was apparently examined by his mother who noted that he was "a goodly child" (Exod. ii. 2). Possibly this examination referred to viability, for such scrutiny of a newborn is unprecedented. On the other hand, it is possible that he was simply a "good child" and lay quietly, so that there were no cries from him to indicate to the Egyptian spies that a Hebrew infant had been born—such infants, if masculine, having to be drowned on the instructions of Pharaoh. Being a "good" baby, he could safely be hidden for a few months. Taking the other view, the fact that he was secreted for three months may indicate that he could safely be hidden for that period since the Egyptian spies did not expect his mother to be delivered three months early, and would therefore not be expected to call at the household until the expected date of delivery. Being thus three (lunar?) months premature, he was therefore closely examined by his mother and found to be viable.

Death in early neonatal life is noted in

1 Kings iii. 19, while Judges xx. 15–16 relates the doubtful occurrence of Erb's palsy in infants (Brim, 1943). The resuscitation of the neonate is alluded to in the biblical commentary concerning the two chief midwives of Egypt—Puah and Shifrah (Exod. i. 15). While the meaning of Shifrah has been considered to be "cleaning" (the newborn?) (Brim, 1936), another view holds that it is derived from the term "shefufereth" meaning "a tube", since it was customary among stillbirths for the midwife to insert a reed into the throat and to blow down it, in the hope of reviving the infant (Zimmels, personal communication). The Babylonians are known to have practised intra-oral breathing as a means of resuscitation (Castiglioni, 1949). The term "Puah" means "to comfort" (the mother?) or "to whisper lovingly" (to the infant?) (Brim, 1936). A further view is that "Shifrah" means "beauty" and that "Puah" is related to an Ugaritic word meaning "a free-born girl of marriageable age but still living in her father's house" (van Selms, personal communication).

A number of delightful legends have been told and retold concerning the embryo and newborn. At the moment of conception, Lailah, the Angel of the Night, takes up the fertilized ovum to God, who decrees its qualities, characteristics and future, only piety or wickedness being left to be determined by the individual himself. Then God brings a reluctant soul from the seventh heaven and forces it to enter the embryo. Thereafter Lailah once more carries this embryo with soul back to the womb of the woman (Ginzberg, 1956).

Not unexpectedly, many of the biblical worthies possessed remarkable qualities at birth. Whereas all living things had been brought into being by the *word* of God, Adam was created by his very hands. Hence he first appeared as an adult. In the idyllic period prior to the flood children were born after but a few days pregnancy, and were so mature that they assisted at severing the umbilical cord, could talk and walk, and had no difficulty in overcoming the demons who sought to molest them. Cain could run at birth. When Noah was born he praised the Lord. Abraham grew to adult proportions within twenty days of his birth. Yochebed, mother of Moses, being entirely without blemish, was not subject to the curse of Eve, and had her children without distress. When Moses was born, he could walk and talk. Indeed, like ben Sira, he refused his mother's milk (Ginzberg, 1956). Jesus also spoke at birth.

In closing, we can do no better than to quote from the cavalcade of birth as noted in the apocryphal work (*c.* 50 B.C.) of The Wisdom of Solomon (vii. 1–6):

I myself also am mortal, like to all,
And am sprung from one born of the earth,
The man first formed,
And in the womb of a mother was I moulded
Into flesh in the time of ten months,
Being compacted in blood of the seed of man
And pleasure that came with sleep.
And I also, when I was born, drew in the common air,
And fell upon the kindred earth,
Uttering, like all, for my first voice, the self-same wail:
In swaddling clothes was I nursed, and with watchful cares.
For no King had any other beginning,
But all men have one entrance into life,
And a like departure.

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ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

SUSSEX PLACE, REGENT'S PARK, LONDON, N.W.1

SCHOLARSHIPS, LECTURESHIPS AND PRIZES

available in 1961

for which application must be made in 1960

THE appointments will be made by invitation of the President and Council of the Royal College of Obstetricians and Gynaecologists at the November, 1960, meeting of the Council.

1. The William Blair-Bell Memorial Lectureships.
2. The Bernhard Baron Travelling Scholarship.
3. The Edgar-Gentilli Prize.
4. The Green-Armytage Short-term Travelling Scholarship.

WILLIAM BLAIR-BELL MEMORIAL LECTURESHIPS IN OBSTETRICS AND GYNAECOLOGY

The conditions of these appointments according to the bequest are as follows:

(i) Two lectures only may be delivered in each year.

(ii) The Lecturer must be either a Member of the Royal College of Obstetricians and Gynaecologists or a Fellow of not more than two years' standing. If the Council of the College think fit, two Lecturers may be chosen.

(iii) The subject or subjects of the Lectures must be either Obstetrics or Gynaecology, or closely related thereto. In the selection of the Lecturer or Lecturers, preference will be given to Lectures embodying original work, particularly in regard to the morphology, physiology and pathology of the female reproductive organs, but this condition need not be considered an absolute condition of the appointment, particularly if the alternative be a problem connected with malignant neoplastic disease.

The honorarium for each of the two Lectures is twenty-five guineas.

Recommendations or **applications,** accompanied by a short précis of the proposed Lecture, must reach the Secretary not later than **1st August, 1960.** The précis should bear a nom-de-plume.

BERNHARD BARON TRAVELLING SCHOLARSHIP IN OBSTETRICS AND GYNAECOLOGY

This Travelling Scholarship in Obstetrics and Gynaecology has been endowed by a generous gift from the Bernhard Baron Charities Trust. The amount available will be £500. It is open to any Fellow or Member of the College.

In making application, the candidate must state his qualifications and experience and detail his suggested programme. The names of two referees must be given.

The successful candidate will be required to give an undertaking that he will complete his programme within a specified time and will furnish a full report on completion.

Applications must reach the Honorary Secretary not later than **1st August, 1960.**

THE EDGAR-GENTILLI PRIZE

Through the generosity of Mr. and Mrs. Edgar, the Council is also able to offer annually a prize of £100, this to be known as the Edgar-Gentilli Prize. The award will be made in recognition of original work on any aspect of the structure, function and pathology of trophoblast and the placenta, and particularly of any original work which has a direct or indirect bearing on the causes and treatment of hydatidiform mole and chorion epithelioma.

The results of any research work in this field can be embodied in the form of an essay or article in English not yet published by the candidate. Candidature is not restricted to Fellows and Members of the Royal College of Obstetricians and Gynaecologists.

Applications should be sent to the Secretary on or before **1st August, 1960.**

THE GREEN-ARMYTAGE SHORT-TERM TRAVELLING SCHOLARSHIP FOR 1961

Through the generosity of Mr. V. B. Green-Armytage the Council is able to award a Scholarship to the value of £75 to a Fellow or Member of the College.

Applicants should have shown a special interest in some particular aspect of obstetrical or gynaecological practice. It is the donor's wish that the award should be used if possible to visit a centre where similar work is being carried out.

Applications for the award should state:

(*a*) The appointment now held.

(*b*) The subject of study and information of any work already published, or in course of preparation for publishing.

(*c*) The centre which it is desired to visit.

The successful applicant will be required to furnish the Council with a report on his visit within a specified time of the grant of the award.

Applications must reach the Honorary Secretary not later than **1st August, 1960.**

S. J. CAMERON

Obituary

S. J. CAMERON

LL.D., M.B., F.R.F.P.S., F.R.C.O.G.

PROFESSOR CAMERON, emeritus professor of Midwifery in the University of Glasgow, died at his home, Stobieside, near Drumclog, Lanarkshire, on 29th October, 1959, in his eighty-second year.

Samuel James Cameron, son of Professor Murdoch Cameron, one of the pioneers of Caesarean section in this country, was born in Glasgow on 7th January, 1878. He was educated at Millhill School, and graduated in medicine at Glasgow University in 1901. After holding the usual resident appointments and acting as Demonstrator in Anatomy for two years, he spent twelve months as House-surgeon in the Chelsea Hospital for Women in London. There he studied under Bland Sutton, Berkeley and Bonney, and formed a life-long friendship with them and many of their contemporaries.

Soon after his return to Glasgow he joined the Staff of the Western Infirmary and the Royal Maternity Hospital, and in due course became the Chief of a Unit in both of these institutions. Later, from 1935 to 1942, he occupied the Regius Chair of Midwifery at the University.

For almost half a century he was one of the most distinguished and best-loved members of the medical profession in Scotland, and among the obstetricians of the Glasgow School his name is already a legend. It will long remain so, being kept alive by many stories recalling his clinical acumen, his masterly surgery, lucid teaching, ready humour, and even his attractive mannerisms. And it is significant that in these tales he is always referred to simply as "Sam Cameron"—a tribute to his outstanding abilities which made titles superfluous, and a mark of affection for the man himself. To his former house-surgeons and assistants his death has brought a sense of personal loss, their initial hero-worship of the dexterous operation having changed with the years into a deeper and abiding veneration. No chief was more generous to his juniors, or allowed them more scope or freedom of action. This was indeed his deliberate policy, for in this matter, as he himself explained, he decided to follow Dr. Arnolds' plan of "trusting the sixth form".

His skill and judgment were widely recognized, and for many years no visiting society ever came to Glasgow without going to see him operate. He loved operating, revelling in the use of every technical device and expedient such as hemisection of the uterus, and he obviously enjoyed his ability to work at great speed. But it is a mistake to think, as some people suggested, that he regarded speed as an end in itself. On the contrary, he repeatedly warned his assistants against this fallacy, and impressed on them that the essential basis of all good surgery is simplicity of method and a sound knowledge of anatomy and pathology.

In the early stages of his career he himself devoted much time to the investigation of such pathological conditions as adenomyosis; the degenerations and complications of fibromyomata, fibroids in unusual situations, extrauterine pregnancy, endometritis, and malignant tumours of the ovary. His later communications dealt mainly with the operative treatment of prolapse, contracted pelvis, Caesarean section, rupture of the uterus, the management of concealed accidental haemorrhage, and the treatment of puerperal sepsis. For the benefit of his students he also published *A Manual of Gynaecology* and (jointly) *A Glasgow Manual of Obstetrics*, a monograph on "Uterine Haemorrhage", and one on "Difficult Labour".

He soon built up a large and far-flung private practice, and rather paradoxically it was his private work that led directly to his greatest contribution to the general public. For in the course of his journeys to patients all over the country, he noticed that in several regions there were virtually no obstetric facilities whatever, and he set himself the task of remedying this defect. He began by paying weekly or fortnightly visits to one of the small hospitals in these areas, and conducting out-patient clinics and operating sessions. Before long the local general practitioners, and later the local health authorities became interested in the project, and in the fullness of time there developed the excellent obstetric and gynaecological services which now exist around the town of Perth, in the county of Lanark, and in the wide stretch of country between Carlisle and Stranraer.

Despite his heavy commitments he found time for an extensive range of interests. He was particularly fond of shooting, fishing and tennis; he studied wild-life in all its forms; he read widely, especially works on history and folk-lore; and he was a connoisseur on antique furniture, silver, etchings, mezzotints and oils. His lovely home was filled with perfect specimens of all such works of art, and he never tired of showing them to anyone who was interested and sharing their beauty with all who visited him.

He had many visitors, for he was an excellent host and his wife a most charming and gracious hostess. The whole year round they welcomed an endless stream of guests to house parties, dinner parties, garden parties and the like, and many generations of house-surgeons look back with pleasure to the happy week-ends they spent at Stobieside. There were long walks over the moors and along the hill-burns, there were countless animals to be seen too, horses, ponies, tortoises, rabbits, pigeons, and dogs of every size and shape. And there was tennis—from earliest spring to the onset of winter—except on Sundays. By Dr. Cameron's express command the court stood empty on the seventh day lest the feelings of the local inhabitants should be offended—for the battlefield of Drumclog with its sad little monument lies within sight less than a quarter of a mile away, the spirit of the martyrs lingers to this day over these wind-swept moors, and the farmer folk of the neighbourhood still worship a jealous God.

For over forty years Dr. Cameron had his country house within a few miles of Smellie's birthplace, and it was therefore almost inevitable that he should have become an authority on the life and work of this master of obstetrics. It is largely due to his enthusiasm and exertions that the Smellie Library is now suitably housed and that the Obstetrical Societies of Edinburgh and Glasgow combined to secure the renovation of Smellie's tomb and its protection for all time by the erection of a stone building around it. And to him alone belongs the credit of the establishing and naming of the William Smellie Memorial Hospital at Lanark. The foundation of this hospital gave him untold pleasure which he tried to express by the personal gift of the lovely bronze statue of mother and child which he commissioned Peploe to make and which stands in the hospital grounds.

But the greatest of all his pleasures was undoubtedly his home. No man had a happier married life or family life than he. He is survived by his widow, a son, three daughters, and several grandchildren. To them we extend our sympathy.

JOHN HEWITT

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

AT the Meeting of Council held in the College on Saturday, 28th May, 1960, with the President, Sir Andrew Claye, in the Chair, the following were elected to Council to fill statutory vacancies:

As representatives of the **Fellows:**

LONDON	John Campbell McClure Browne. Stanley George Clayton.
ENGLAND AND WALES (excluding London) ..	Francis Edward Stabler.
SCOTLAND	Robert James Kellar.
NORTHERN IRELAND AND EIRE	Gavin Boyd.

As representatives of the **Members:**

LONDON	John Stanley Tomkinson.
SCOTLAND	Wallace Barr.

The following were admitted to the **Fellowship:**

George Henry Bancroft-Livingston.
Marjorie Olive Bennett.
Mary Ardelice Murray Bigby.
George Wills Blomfield.
Joyce Muriel Burt.
William Stewart Campbell.
Edward Cope.
Henry Vincent Corbett.
George Archibald Craig.
David Alfred Davies.
Nagal Subhadra Devi.
John Geoffrey Dumoulin.
John Paton Erskine.
John Burns Farquhar.
Guy Beadon Walmsley Fisher.
Alan Macpherson Giles.
Thomas Ayton Gillie.
Alan Mostyn Bradford Grant.
Arthur St.G. McC. Huggett.
Lois Edythe Hurter.
David Worsley James.
Mary Kathleen Lawlor.
Ronald Fox Lawrence.
John Bateman Lawson.
David Hugh Lees.
Lorna Lloyd-Green.
George Ian Louisson.
Roderick Hector Macdonald.
Agnes Rose Macgregor.
Kenneth McIver MacKenzie.
Cecil John Mackinlay.
James Theodore Mair.
Robinson McIndoe Millen.
Gardiner Mitchell.
Philip Rene Mitchell.
Frank Lionel Edward Hugh Musgrove.
Premavathi Maddimsetti Naidu.
Michael Kieran O'Driscoll.
Edwin Ronald Ormerod.
John Henry McKnight Pinkerton.
Eric Eli Rawlings.
Donald Norman Struan Robertson.
Charles Victor Salisbury.
Choudhuri Abdus Samad.
David Arnold Fletcher Shaw.
Norman Graham Guy Talbot.
James Macbeth Thomson.
Ramsay Warden.

The following were admitted to the **Membership:**

Armaity Aspandiar Anklesaria.
Alison Margaret Armstrong.
Maxwell Philip Awon.
Pamela Mary Bacon.
Amarendra Banerjee.
Gerald Stuart Banwell.
James Drummond Begg.
Kwesi Kobea Ogoe Bentsi-Enchill.
Ajilady Savithri Bhandary.
Kevin Godfrey Bland.
Kathleen Angela Scott Brosnan.
George Rennie Brown.

Solomon Burgin.
Biman Kumar Chakrabarti.
Harry Cohen.
James Brendan Comerford.
Frederick George Cox.
Gerda Jane Crow.
Moolman Meyer de la Harpe.
Ronald Alexander Don.
Sheila Longmuir Black Duncan.
Solomon Ende.
Alasdair Campbell Fraser.
Peter Hardwick Foote.
Keith Edgar Free.
Ian King Furler.
William Terence Gallagher.
Susan George.
Ronald Giles.
Christopher Stratford Harison.
Patrick Desmond Hill.
Uriah Jacobson.
Snehalata Bhujanga Kamath.
Pun Shui Kan.
Swadesh Kumari Kataria.
Brendan Keane.
Bhagwanti Gobindram Kotwani.
Ariffin Bin Ngah Marzuki.
Tanendra Nath Mitra.
Thomas Khoon-Fong Ng.
David Bernard Paintin.
Heather Maureen Panton.
Mary Caffyn Wright Paterson.
Ellis Charles Pixley.
George Lloyd Sinnett Rankin.
Lionel Joseph Schewitz.
Stanley Clifford Simmons.
Nargese Jehangir Talati.
Edgar Patrick Wylie Tatford.
Brenda Anita Taylor.
Molly Ethel Towell.
Mary Monica Tyndall.
Robin John Venn.
Norman Fulton Walker.
William Allen Willcox Walters.
David Knapman Williams.
Liam Hugh Wright.

List of Candidates who have been awarded the **Diploma in Obstetrics:**

Margaret Edith Abel.
Shirley Ann Pamela Abell.
Eleanor Mary Adams.
James Frederick Renwick Adams.
Alexander Addison.
Delia Montgomery Aitken.
Razia Akbani.
John Amstrong.
John Richard Ashwood.
Derek Atkinson.
Frank Gordon Atkinson.
Safiya Azimuddin.
James Kirk Baird.
Robert Baird.
Ramala Bakaya.
Peter John Ball.
Roderick Martin Barnes.
Maureen Elspeth Barr.
Dennis Graham Barrowcliffe.
Ivy Barua.
John Francis Sewell Batson.
John Trumpler Bavington.
John Ruddick Bell.
Marc Sylvio Benett.
Richard Boyd Bennet.
Michael James Peter Berkley.
Leopold Stuart Bernstein.
Frederick Ashley Best.
Gordon James Biggam.
Margaret Anne Birchall.
Terence Alexander Paul Birkett.
Henry Edward Black.
Paula Dorothy Black.
Margaret Isobel Blackhall.
Harold Raymond Blair.
Archdale John Blakeman.
James Rawson Blatch.
Alfred Ian Blenkinsop.
Reuben Bolton.
Geoffrey Tregarthen Killeen Boughey.
Charles John Briglmen.
James Michael Bristow.
James Brosnan.
Alan Harvey Brittain.
Henry Christopher Illingworth Bywater.
John Rowell Burwell.
George Leslie Caley.
Ian Capperauld.
Conor John Carr.
John Vaughan Forbes Catto.
Alexander John McMurrough Cavenagh.
Edwin Christopher Cawte.
Theam Kheng Cheah.
Joseph Patrick Ah Fee Chui Wan Cheong.
John Martin Clark.
Colin Boris Clennar.
Marjory Clowsley.
James Halliday Cochrane.
Michael David Coulter.
Izette Rosemary Coulton.
Garth Forrest Counsell.
George Cowie.
John Coyer.
Timothy Agatine Crantock.
Alistair Daniel Crawford.
Alison Sweet Escott Crewdson.
Katharine Elizabeth Cuthbert.
Peter Gordon Dale.
Shyamoli Datta Chowdhury.
Denzil Davies.

Gwyneth Mary Davies.
Huw Thomas Davies.
Leon Malcolm Davis.
John Alan Davis.
Brigid Catherine Clare Davison.
Hugh Dawson.
Lalita Vishnupant Deshpande.
Charles Diamond.
William Robert Dick.
Brian Cedric Dixon-Warren.
Phyllis Eleanor D'Netto.
Kevin Edward Doran.
George Stewart Duncan.
Harold James Henry Dunn.
Douglas Eakins.
Vasos Andrea Economides.
Elizabeth Marjorie Edmunds.
Joshua Gerwyn Elias.
Elizabeth Elliott.
Peter Jonathan Ellis.
Robin William Elsdon-Dew.
Leonard Abosede Emanuel.
Peter John Enoch.
Caryl Donough Geraint Evans-Prosser.
Michael William Everitt.
David Red Farmer.
Barry Erle Farnham.
Lewis Jesse Farrow.
Biyagamage Aaron Fernando.
Nurjahan Ferozuddin.
Hans Werner Fladee.
Ivor Maxwell Fletcher.
Janet Anne Fletcher.
Kevin Flintan.
Henry Brian Bayley Forshaw.
William Fox-Russell.
Herbert John Lewis Francis.
Peter Ivan Frank.
Adam Kelso Fulton.
Nigel Hedley Noall Gardner.
Peter Tom Gardner.
Ramon Gardner.
Arthur James Alfred Garlant.
Thomas Henry Geddis.
Jennifer Mary Rae Gilchrist.
Albert Alan Gildersleve.
Patrick Geoffrey Gillam.
Patrick John Gillies.
Robert Thom Glen.
John Edward Godrich.
Harry Leon Goldwater.
Derek John Goodman.
Ian Stewart Governor.
Charles Baring Travers Grant.
Ellen Catherine Gardner Grant.
James Niall Stevenson Green.
Robert Culross Grieve.
Monica Mary Gurnhill.
Savitri Gurung.
Desmond David Guy.
Colin Andrew Assheton Haigh.
Keith Colin Hammond.
Margaret Edith Hanlon.
David Ronald Wallen Hartley.
Donald Charles Harvey.
Beryl Heap.
William Ralph Heaton.
Ronald Heslop.
Anne Shirley Hill.
David Moore Cameron Hislop.
Edward James Horgan.
John Lister Horner.
Geoffrey Raymond Horton.
Janet Mary Houlston.
Judith Catherine Howard.
Mary Sophia Howell.
Khin Khin Htway.
Huw Idris Humphreys.
Graham Bernard Hunt.
Florence Suhasini Iswariah.
Irene Margaret Janie Jackson.
Trefor Jenkins.
Howard Colin Jennings.
Herbert Hugh John.
Saramma John.
Alan David Shore Johnson.
Richard Wynne Jones.
Vyvyan David Jones.
Mary Olivia Joseph.
Haddad Omer Karoum.
Audrey King.
Harold Jack Kosasky.
Sylwester Krzaniak.
Iain McAlpine Kyles.
Harry Ormrod Latham.
Anthony Bannerman Lavelle.
Andrew Raymond Leader.
Eva Hanna Letchner.
Leslie Lewis.
Thomas Lind.
Rhona Lindup.
Henry Knowles Litherland.
Nesta Elizabeth Lloyd.
John Alfred London.
Conn Lucey.
Grania McCarthy.
Shaun Francis McCarthy.
David Richard McCoy.
James Spowart McCracken.
Kennedy Henry McCraith.
Alan Hector Macdonald.
Bernard Michael McGibbon.
Robert Douglas Macgill.
Duncan Buchanan MacGregor.
Daniel McLeman.
June Margaret McLeod.
Ian Scott Macmillan.
Alexander Duncan McNeill.
John Mitchell Maguire.
Frances Shao Fen Mao.
John Martin.
John Mason.

Barrington Sherwood Mather.
Gul Mathew.
Ma Tin May.
Martin Anthony Melsom.
Peter Henry Merry.
John Cedric Merrington.
John Miller.
Margaret Katharine Miller.
Patricia Anne Raeburn Miller.
Alan Ramsay Milne.
Colin Askew Milner.
Brian Aubrey Edwin Mindham.
Zakia Minhas.
Andrew Victor Mitchell.
Katherine Mary Moore.
David James Moorhouse.
Henry Miles Moorhouse.
Denis Harry Morgan.
Anthony Brian Morphy.
John Lang Morrison.
Bhati Mukherjee.
John Percival Mumford.
Donald Forrest Munro.
Murdoch Murchison.
Koshu Vishindas Narumalani.
Marjorie Stella Newton.
William Patrick Lawrence O'Driscoll.
Stuart Samuel Ireland Parker.
Harry Vaughan Parry.
Mary Wyn Parry.
Alastair George Peter Paton.
Peter William Scott Patton.
George William Peacock.
James Leith Penny.
James Herbert Perry.
Mary Philipose.
Roderick Michael Phillips.
Raymond Pilkington.
Arthur Joseph Pim.
Sylvia Joan Pinder.
Howard Dudley Ward Plowright.
Mary Spencer Plumbly.
Donald Powell.
Conrad James Primmer.
Dacre John Herbert Prosser.
Ronald Leslie Pyle.
John Draper Raiman.
Chitra Rao.
Maurice John Raphael.
Leonard Rountree Redman.
Marguerita Regan.
Elizabeth Mary Riddell.
Colin John Roberts.
Kenneth Kenmure Thomson Robertson.
Keith Douglas Robinson.
Fitzjames David Roche Kelly.
Lionel Clifford Rose.
David Francis Rowlands.
Satyavathi Roy.
Indu Bhusan Roy Chowdhury.
David George Leopold Kellot Russell.
Ian Alexander Ruthven-Stuart.
Matthaeus Erasmus Richard Samson.
Algine Miliana Sansoni.
Harendra Nath Sarmah.
James MacDonald Scott.
Robin Stuart Charters Scoular.
Antony Maurice Segal.
Cedric Angus Selway.
Ronald Albert Sharpe.
Melvin Clifford Sharrard.
Martin Grenvil Shelton.
Kenneth Ian Shimmings.
Joyce Kamalini Siromoni.
Bruce Alexander Murison Smith.
Robert Newton Smith.
Stanley Sorkin.
Frank Meldrum Spence.
Peter Dennis Sprackling.
John Anthony Stainton-Ellis.
John Tytler Stewart.
Kyu Kyu Swe.
Ernest Taylor.
John Gwyn Thomas.
Anne Elizabeth Treharne.
Michael Elmitt Tuck.
John Lawson Tuton.
Jerome Christopher Twomey.
Victor Ronald Twyman.
Ian Henry Mitford Veitch.
Julian Viner.
Umathevan Viswalingam.
Roy Oliver Walker.
Sheila Jean Wallace.
Michael Thomas Ward.
Alan Ferrier Watson.
Nancy Margaret Watts.
John Louis Webster.
John Weston.
Barry Reid Wheeler.
David Mitchell Whiteford.
Nora Ellen Wild.
Roger Essery Wild.
Michael Charles Thomas Wilkes.
Richard Keith Wrennall.
Alexander Finlay Wright.
Oon Hock Yeo.
Carmen Ka Man Yuen.

REPORTS OF SOCIETIES

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

OCTOBER 1959

A meeting of the North of England Obstetrical and Gynaecological Society was held in Liverpool on the 23rd October, 1959. The President, Mr. Agar, was in the Chair.

Mr. D. W. Currie presented

SOME COMMENTS ON THE TREATMENT OF STRESS INCONTINENCE

When prolapse is present in association with stress incontinence the rational treatment is a repair operation, and in the majority of cases the symptoms will be cured. Mr. Currie had been introduced to gynaecology by Professors Oldfield and Gough. Both were excellent surgeons, one performing the repair with meticulous care, and the other using a large Hagedorn needle with speed and facility. Few patients then complained of stress incontinence, perhaps because they were more tolerant of the disability.

Gough, during the course of the prolapse repair, would remove the tag of fibrous tissue often found at the lower end of the anterior vaginal wall just above the meatus, for aesthetic reasons. He would also demonstrate the urethrocele, and took care to lift this with a mattress suture. Not many patients returned with their symptoms unrelieved, but if they did, they were treated by a small plastic repair, cautery to the urethra, a ventri-suspension or a Hodge pessary.

Though at first Mr. Currie had used Gough's technique, he became more aware of the complaint of stress incontinence, and took more trouble to demonstrate it. In technique he made sure that when the work on the cervix had been completed, the uterus could no longer descend and the uterus was anteverted. Further, he made use of Gough's skin tag, and after its removal he cut into the fibrous tissue on either side of the urethra, and then drew it together with two small mattress sutures, later sewing up the vaginal skin vertically. Though these small points certainly improved the results, there was not complete success with regard to stress incontinence.

Women were now no longer willing to put up with their disabilities, or wait until their child-bearing years were over, and for these reasons the "Wedge Resection of the Cervix" operation was devised. The bladder is freed from the cervix, a wedge removed from the anterior lip, and by stitching the uterus is anteverted, and particular care is exercised in placing the stitches about the cervix and bladder neck.

About this time many new operations were introduced for the relief of stress incontinence, and there was work on the loss of the posterior urethro-vesical angle. Though Mr. Currie had tried these operations, he felt sure that his failures with a vaginal repair operation were due to lack of care with the details and not the fault of the operation as a whole. It was also necessary to make sure that the complaint was stress incontinence and not some other difficulty in micturition. The operation of Wertheim's hysterectomy is associated with great disturbance of the anatomy of the bladder, and in 2 of 5 such cases cystography showed the bladder had fallen back creating a marked angle with the urethra. Two patients were treated by passing a fascial sling round the urethra, and three were successfully treated by a small repair limited because of the previous operation.

The rational treatment of the bulk, if not all cases of stress incontinence, is a plastic operation from below, and, if this fails, it is usually due to some error in surgical technique. In the treatment of uterine prolapse it should be emphasized that, when the work on the cervix is completed, the uterus should be anteverted. The bladder must be pushed well off the anterior wall of the cervix, and the lateral ligaments must be inserted into the anterior aspect of the stump. A long anterior vaginal wall should be created and supported with mattress sutures to hold the bladder and urethra close to the symphysis. The mattress sutures should be small and numerous rather than large and few, and the urethra should be slightly constricted just above the meatus. The repair of the posterior vaginal wall is also essential.

Discussion

The President thought that in Leeds the repair operation was regarded as the method of choice.

Dr. R. Newton promised to write a paper himself. Even when he started gynaecology, stress incontinence was recognized and Sir William Fletcher Shaw inserted Kelly's sutures. Professor Dougal did many of the things Mr. Currie recommended, including repair of the posterior vaginal wall. A well-performed colporrhaphy is the operation of choice and further procedures are seldom needed. Of these Bailey's procedure is the most logical. Of 20 patients operated on in 1955, all are satisfied though 2 get stress incontinence on severe coughing. The elderly patient is a particular problem as a sling may in later years be a barrier to micturition. In some cases there may be a discrepancy between X-ray findings and symptoms.

Dr. K. V. Bailey found that what Mr. Currie was saying was that a properly carried out Manchester operation would cure stress incontinence. He did not

favour mattress sutures as they might drag out the distal urethra. When investigating 800 cases he carried out the same technique, and 30 per cent were not cured. His investigations showed a high degree of conformity between the posterior urethro-vesical angle and stress incontinence. There are, however, degrees of stress incontinence, and varying degrees of stress.

Dr. E. A. Gerrard uses mattress sutures, and they need not shorten the vagina. Unless the uterus becomes anteverted as the Fothergill stitch is tightened, it never will be. A second vaginal repair should always be done if the first fails.

Dr. W. Calvert found he could decide clinically if the vaginal approach would be successful.

In reply Mr. Currie had one comment: none of these things are new. The vaginal repair was a very good operation and an indication of the gynaecologist's skill.

Professor C. Scott Russell showed a film

THE DIFFERING MANAGEMENT OF SEVERE INJURY TO THE URETHRA AND BLADDER NECK

The film illustrated some aspects of the management of about 70 cases of fistulae.

Dr. D. W. Warrell described the

PITFALLS OF CYSTO-URETHROGRAPHY

Fundamentally the technique of cysto-urethrography is simple. The bladder is outlined by radio-opaque fluid and 3 films are taken—at rest, when straining and during micturition. The interpretation of these films and the correlation with a particular clinical lesion are difficult, and it is first necessary to establish the effect of variations in technique, and the range of appearance in women with normal urinary control. The disadvantage of the antero-posterior view is that if a cystocele is present it obscures the important region of the bladder neck. Oblique views are difficult to orientate and interpret, but the lateral view gives a clear outline of the bladder neck.

It is claimed that a well-marked urethro-vesical angle is characteristic of normal urinary control, and funnelling of the proximal urethra and prolapse of the bladder neck have been cited as characteristics of urinary incontinence. There are, however, several ways in which variations in technique may affect these appearances.

If too much radio-opaque fluid is run into the bladder, or if it is cold, it may irritate the bladder, and dilatation of the proximal urethra and flattening of the posterior urethro-vesical angle are produced. A large stiff catheter will do the same. Sodium iodide sometimes irritates, increasing detrusor tone and flattening the posterior urethro-vesical angle, and in obese women barium produces a better contrast.

The position of the patient may affect the X-ray appearances. The general effect of the sitting position is to flatten the urethro-vesical angle. Though the amount of bladder neck prolapse is not influenced by variation in technique, it is under the control of the patient, and the frightened patient will not strain.

Thirty-eight patients with normal urinary control have been investigated, only 2 of the 14 patients with prolapse showing loss of the posterior urethro-vesical angle. Of the 24 women without prolapse, the angle was absent in 5. The careful attention to detail in the technique, and the wide variations in the normal patient were emphasized.

Discussion

Mr. D. H. Lees had found so many pitfalls in assessing X-rays that he had begun to examine the urethra with a urethroscope, and investigate the intravesical pressure with a manometer. This could make a rewarding study, and it might show that the posterior urethro-vesical angle is not so important, but that prolapse of the bladder mucosa into the urethra was an essential feature.

Dr. W. Hunter read a paper on

THE RECTO-VESICAL LIGAMENT

(This article appears on page 429 of this issue)

The discussion was limited by inadequate time.

Mr. D. H. Lees had recently performed a Caesarean section. The rectum and bladder were close together, and there was a wide recto-vesical band indicating failure of separation, but the operation had not been difficult.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

DECEMBER 1959

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Leeds on the 18th December, 1959. The President, Mr. H. Agar, was in the Chair.

Mr. R. G. Denniss reported a case of

SUCCESSFUL PREGNANCY FOLLOWING TREATMENT FOR PELVIC TUBERCULOSIS

(This article appears on page 434 of this issue)

Discussion

The President commented on how unusual it was for a patient with pelvic tuberculosis to recover and become pregnant.

Mr. W. Hunter asked if there were any toxic effects from the treatment.

Dr. R. Newton enquired if there was evidence of tuberculosis of the endometrium.

Mr. P. Malpas asked if the tuberculosis was human or bovine.

Mr. T. B. FitzGerald thought that treatment should either be radical or conservative, and that it was not good policy to remove only one tube.

Mr. T. F. Redman had seen no sinus develop following surgery since streptomycin treatment had been instituted.

Mr. G. A. Craig reported a case of bilateral tuberculous salpingitis on whom he had performed a salpingostomy, streptomycin was given, and she had since had a child.

Mr. D. W. Currie had noticed that caseation in a Fallopian tube always diminished towards the uterine end. He excised the tube until healthy tissue was reached sometimes leaving only ½ inch, and 5 patients had since become pregnant.

Professor C. S. Russell asked what factors precipitated the tuberculous meningitis and Dr. N. Lissimore thought it was iatrogenic.

Professor T. N. A. Jeffcoate congratulated Mr. Denniss on the presentation and Mr. Agar on the management. There are cases where tissues are so damaged they must be removed, but with the widespread peritoneal tuberculosis there was no point in doing more than salpingectomy. He had seen only one case where healing of the abdominal incision was not by first intention, and no case of fistula, despite all degrees of advancement of the disease.

In answer Mr. Denniss said there was no toxic effect from treatment, and the endometrium was not studied as abortion was in progress. He defended the conservative surgical approach as peritoneal spread was advanced.

Mr. H. Agar delivered his presidential address on

The Development of Some Surgical Instruments and Appliances

The origin of most mechanical appliances made to assist the surgeon can be traced far into antiquity. The first tools were made of bone or horn, used as weapons or for stitching hides, but probably man's own teeth and finger nails were his sharpest tools. The earliest cutting edges resulted from the accidental fracture of stone, especially flint, and as time went on handles were attached.

The oldest code of law—that of Hammendi *c.* 2100 B.C.—gives evidence that metal knives were in use for surgical purposes, and decrees the unfortunate punishment of the doctor should his patient die. In the Temple of Aesculapius there is depicted a case of three scalpels, and it is possible that these instruments were made of steel for the Greeks knew of the process of tempering the metal, and there is little doubt that they used it for cutting instruments. Scalpels of various types were discovered at Pompeii.

Later modifications included the introduction of bone handles in the 14th century, but in the 17th century all-metal scalpels were re-introduced. Later, decoration was added, and a flat ivory handle was often attached.

Along with these developments many larger knives were being produced, and the first description of the amputation of a limb for which they were reserved is to be found in the first century A.D. by Cornelius Celsus. It is clear that the mechanics of the saw were well known at that time and it had probably been discovered many centuries earlier for there is an Egyptian relic in the British Museum dated *c.* 3000 B.C. in which the jagged edge of a flint is set in a wooden haft.

One of the outstanding errors in the history of obstetrics was the belief that the innominate bones separated during labour. This belief persisted until the time of Vesalius in the 16th century. Paneau in 1592 first suggested exaggerating this mechanism, de la Courvec in 1655 attempted the operation immediately after death, and le Roy was the first to perform the operation of symphysiotomy by candlelight at midnight, on a living rachitic dwarf. In Italy and France the operation remained popular, and Gigli in 1893 described the advantages of his serrated wire saw.

Although the hand remains the most useful and effective surgical instrument it needs other aids to develop its maximum efficiency. Hippocrates wrote about the care and use of the hand. Opposition between index finger and thumb probably gave rise to the idea of the forceps, and originally the term "forceps" was applied to a very simple gripping instrument consisting of two legs either bent over in a loop or forged together. Prehistoric forceps were of various metals. Hippocrates mentions the use of bronze, and Aristotle of iron and steel, and the Byzantine physician, Orisbasios, 320–403 A.D., gave an appraisal of the value of bronze against iron.

Although the ancients of the Middle East and Mediterranean countries are given much credit for producing early instruments it seems probable that they had copied Susruta who was a great exponent of Hindu medicine and who preceded Hippocrates by 100 years. He classified many surgical operations and instruments.

The earliest forceps are among the oldest metal instruments and date back to 3300 B.C. They were used for personal toilet or crude operations. Woolley in 1926, when excavating Ur, discovered a case of gold instruments including tweezers, an earscoop and a stilet. Many other instruments from the Samorian period have been discovered in that region.

Forceps were found in Egypt in the tomb of Semerkhet (3300 B.C.). They may have been simply epilation forceps, but perhaps were surgical instruments used for the removal of missiles of war from wounds. Egyptian priests at this time shaved the head and face, and wore wigs, and hieroglyphs and razors have been found in the tombs of the Middle Empire, 2160 B.C.

A famous scroll, named after George Ebers who bought it in Luxor in 1872 and which is now in the Leipzig museum, gives useful information. It is regarded as the correlation of various medical texts, and there is mention of genital prolapse and its treatment by the application of honey and petroleum. Though there is little detail, it is clear that many operations such as herniotomy were known. There is also a direct reference to forceps to pierce the flesh of a swollen limb.

Many mummies have teeth filled with gold and are wearing dental plates, and, as both male and female circumcision has been recorded, it seems likely forceps would be used. About 2000 B.C. forceps appear with the lower ends of the arms turned inwards and the jaws

developed into fine points. In the Bible (Exodus and Isaiah) there is evidence of the use of tongs in the care of fires and lamps but not as surgical instruments. After many centuries we have the Roman period which left behind a rich literature. Toilet sets of *c.* 200 A.D. have been found in London, and a unique specimen found in Kent and dated *c.* 600 A.D. has three legs. Moschion, who lived in Rome in the 6th century, described the use of forceps in the removal of an enlarged clitoris. Other descriptions of the use of forceps come from Aetius, Court Physician at Byzantium, and Galea, 150 A.D., described specialized surgical forceps for use for varicose veins, and how similar is the operation to the modern one of stripping. He mentions various forceps and knives but during all these ages little attention was given to haemostasis.

Although Celsus, A.D. 25, had used ligatures, the practice lapsed until the time of Ambrose Paré, 1515–1590. In order to help him apply the ligature he developed a new type of forceps with a spring to keep it closed. Further developments of the haemostatic forceps were delayed a long time, perhaps because the surgeons or barbers, unable to overcome pain, were forced to operate with great speed. At a later stage the manufacture of instruments passed from the blacksmith into the hands of the cutlers, and the answer to the problem of artery forceps had to await the Listerian antiseptic technique for resolution.

Surgical instrument makers as such did not make their appearance until 1800, and Charniere and L. A. Collins were among the first to show such ingenuity that many advances in surgery were dependent on them. William Taylor, 1866, invented a self-holding vessel forceps with crossed legs, but it was not until 1870 that the ratchet was added, probably by Jules Péan.

Thomas Spencer Wells, born at St. Albans, a general practitioner in Barnsley and partly trained in the General Infirmary at Leeds, designed the instrument that bears his name and published details in the *British Medical Journal* in 1874. He had a varied existence, fulfilling naval duties in Malta, practising ophthalmology in London, before being elected to the staff of the Samaritan Hospital. After serving in the Crimean War, he returned to London and performed his first successful oöphorectomy in 1858. His success was in part due to the rigid discipline he maintained in the theatre. From this time the basic design of modern artery forceps was agreed in the surgical world, yet in the same year J. Y. Simpson was using the simplest of devices to control bleeding—pins of various sizes to press the bleeding vessels against other tissues.

Hippocrates in his writings on "Disease of the Womb" mentions vaginal dilators and leaden sounds to dilate the cervix and to apply medication to ulcerated areas. He also describes treatment for haemorrhoids and cervical polypi. It is probable that the idea of an expanding instrument evolved from the use of the hand for dilatation of the vagina or cervix. The earliest expanding specimens in bronze were discovered at Pompeii which was destroyed in 79 A.D. The speculum is mentioned in the writings of Soranus, of Aetios in 200 A.D. for the treatment of pelvic abscess, and of Albucasis, 1013–1106, the Arabian surgeon. Thereafter for many centuries there was little development until in 1526 Gersdorff described "A speculum that is to open the anus or the birthparts of a woman".

In 1554, Rueff, a Zurich superintendent of midwives, described a speculum to be used when "Children sticking in the womb and being dead are to be brought forth". It is certain that up to this time all instruments for the extraction of the baby such as hooks and crochets were applied to the dead foetus, and by dilating the cervix there was some hope of a living child.

Beaumont, an English surgeon who migrated to Canada, described a speculum in 1837 to aid in operating on fistulae. It consisted of four blades 3 inches long attached at right angles to a metal band. This device approached the tubular speculum which later became popular, but it has an antique origin for it is explained in the Talmud how a woman may discover if bleeding is uterine by introducing a tube into the vagina and through it a cotton tampon. As time passed its popularity increased. In 1855, Robert Fergusson, first Professor of Obstetrics and Gynaecology to King's College, used a straight tubular glass speculum, and, in 1870, Sir William Fergusson claimed the invention as his. In the end the metal type found favour when a lasting polish could be given.

The speculum designed by Sims in 1845 is reputed to have been made first from a bent-over pewter gravy spoon when he forgot his own speculum on a visit to a patient. From this he devised a silver instrument with a polished concavity. Chelius and probably Velpeau, unbeknown to Sims, had been using the knee-elbow position, and Sims also overlooked the reports by Goseth in 1834 and Von Metzmer in 1846. During the next few years Sims found the advantages of the lateral position. He also popularized silver wire sutures, and he chose "Silver suture in surgery" as the subject of his Anniversary Discourse before the New York Academy of Medicine in 1857. Silver wire had, however, been reported in the *Lancet* by Gosset in 1834.

Many other developments occurred, but modern success and the comfort of the operator would not have been so great without the development of rubber gloves. In 1831 the chemist Samuel Guthrie of Sackett's Harbor wrote that he had developed a process for the purification of oil of turpentine, and that it dissolved caoutchouc and dried rapidly. Richard Cooke in 1834 commented in a letter that "a pair of india rubber gloves would be perfectly impenetrable to the most malignant virus". He sent his former professor a nice solution of caoutchouc dissolved in Guthrie's spiritus of turpentine, and made the remarkable suggestion that it would become a useful material in the surgeon's hand, and that he had used it in phlegmonous and erysipelatous inflammations. He added it would be convenient to use in dissecting rooms and in vaginal examinations. Lubricating the hands with it provided an insoluble pair of india rubber gloves perfectly impenetrable to the most malignant virus.

About 10 years later, Thomas Watson (1792–1882), late physician to the Middlesex Hospital, suggested the

use of gloves for antisepsis. He proposed their value in gynaecological examination and child-birth. It seems likely Watson had in mind rubber gloves and he recorded his suspicion that puerperal infection was conveyed by the clothes and hands of the attendant. Those observations appeared about 5 years before Semmelweiss published his observations on Puerperal Fever.

But the use of gloves in operative gynaecology and surgery arose from considerations of a different sort almost 50 years later, and can be attributed to Dr. William Stewart Halsted who wrote in 1913 that in the winter of 1889–1890 the nurse in charge of the operating room complained that the mercuric chloride solution produced dermatitis. He requested the Goodyear Rubber Company to make two pairs of thin rubber gloves. They proved so satisfactory that operator and assistants also wore the gloves. The justification for this procedure was found in the results of a series of hernia operations recorded by Bloodgood in 1899. There were 181 operations with only one case of suppuration. McBurney emphatically favoured them, and thereafter they became more and more popular. It is interesting to note that the apparent protection of rubber gloves is now under suspicion in that about 30 per cent have been found punctured during operation.

Reguier de Graaf, known for his discovery in 1672 of the function of the ovarian follicles, had other mechanical interests. He advised a syringe for the injection of arteries in the cadaver, and in 1668 at the age of 27 he published a monograph on enemata. One appliance he devised was an ox bladder tied to a wooden nozzle and another was a pewter syringe which held about a pint of fluid. Ambrose Paré wrote in 1581 that the syringe was in such common use that it was beneath the dignity of doctors to sully their hands with it and they left it to surgeons. James Primrose defended the clyster as it does not go beyond the great gut.

Against this background de Graaf considered the use of nutrient enemata. He stated that it was impossible to force fluid through the ilio-caecal valve and nutrient enemata should not have ingredients that require digestion in the small intestine. "In cases of advanced pregnancy the value of the clyster must be less since it not only compresses the foetus but it is ejected as if the foetus expelled it." De Graaf also devised an instrument for transfusion composed of a length of intestine of a bird with a duck quill at each end for insertion into the veins.

The flexible tube used by de Graaf may have been similar to the one designed by Caspa Bartholin who was born in Copenhagen in 1655, the son of Thomas Bartholin who was one of a family of 7 brothers and one sister. Of these five became professors in the University. Caspa Bartholin, while a medical student at the age of 19, was appointed Professor of Philosophy. In his apparatus the inside of the tube was made of coiled copper wire fitted with a leather cover. There was little development in this apparatus until Alfred Higginson, who was trained at Liverpool, invented his ingenious system of valves. Following James Blundell, who reported 10 cases of blood transfusion, Higginson revived blood transfusion in Britain, and used his syringe and an average of 12 ounces of blood. The recipient in each case was a woman and it seems likely that the treatment was called for blood lost in association with labour; unfortunately only 2 of his patients survived.

Dr. E. A. Gerrard (Manchester) thanked Mr. Agar for the monumental work of his Address and for all he had done for the Society during his term of office as President. Mr. P. Malpas (Liverpool), Mr. L. B. Patrick (Sheffield), Mr. F. Stabler (Newcastle) and Mr. D. W. Currie (Leeds) added the thanks of their centres to Mr. Agar.

BOOK REVIEWS

"Metabolic Homeostasis." By N. B. TALBOT, M.D., R. H. RITCHIE, M.D., and J. D. CRAWFORD, M.D. Pp. xii+133, illustrated with charts. Harvard University Press (for Commonwealth Fund); Oxford University Press, London. Price 24*s*.

THIS is a neat and lucidly-charted little book written by three paediatricians from the Harvard Medical School. The first half deals with basic considerations of the homeostasis of water, sodium, hydrogen ions, chlorides and phosphorus at all ages. The second section gives the clinical application of this knowledge to infant feeding, renal disorders and parenteral fluid therapy including cases of diabetic ketosis, burns and major gastro-intestinal surgery.

"1959–60 Year Book of Obstetrics and Gynecology." Edited by J. P. GREENHILL. Pp. 573, with illustrations. Year Book Publishers, Chicago; Interscience Publishers, London. Price 60*s*.

DR. GREENHILL's hardy annual is as welcome this year as every year. Whether for the pursuit of a specific problem or for random reading this is an invaluable reference book. To some its main merit is as a mine of potted information on current writings, while others look particularly for the editor's own interspersed comments. This book, this year and every year, is a "must" for the bookshelf of every obstetrician and gynaecologist.

S. Bender

"An Introduction to Gynaecological Exfoliative Cytology." By WINIFRED LIU, M.Sc., M.D., with a Foreword by RUTH M. GRAHAM, Sc.D. Pp. xi+127, with 44 figures. Blackwell Scientific Publications, Ltd., Oxford, and Charles C. Thomas, Springfield, Illinois, 1959. Price 48*s*.

THIS is a short concise book intended as an introduction to vaginal exfoliative cytology for student technicians. There is no similar book on the market and its publication was meant to satisfy a great need in laboratories engaged in the training of cytological technicians. Unfortunately this little volume does not fulfil this purpose.

Cyto-technicians have to be trained in the techniques of smear preparation and screening of slides. They have, therefore, to become familiar with the apparatus for taking specimens, fixing and staining slides as well as with the various aspects of normal, abnormal and cancer cytology.

Winifred Liu's book is subdivided into 12 sections and each of these gives a very superficial insight into the subject. While the chapters on the anatomy, histology, endocrinology and physiology are adequate and well written in simple language the practical chapters on smear taking, fixing and staining leave much to be criticized; e.g., while smear-taking techniques are briefly mentioned there is no single illustration of the apparatus in use and no instructions for sterilizing and storing equipment are given. The few lines on fixation of slides are dogmatic and far from covering the essentials of the subject and the chapter on staining procedures contains nothing more than the description of Papanicolaou's original technique. No mention of other staining methods such as the Schorr stain or more complicated procedures is made.

While the description of the normal constituents of vaginal smears is good the photographs are in black and white and lack definition. No photographs of smear patterns, e.g., cyclical patterns, atrophic patterns, pre-pubertal patterns, etc., are shown and no illustrations of smears obtained by other means than vaginal aspiration are presented.

The greatest shortcoming of this book is the deliberate omission of cancer cytology. Since its purpose is to acquaint the student technicians with the cells they are likely to encounter when screening slides, it seems difficult to understand why the description and illustration of malignant and other abnormal cells have purposely been excluded.

The addition of a gynaecological dictionary to the book will be considered very convenient by most novices in gynaecological laboratories, but since this information can easily be obtained from medical dictionaries it would have been more appropriate to enlarge on the subject proper and to supply sadly missing essential information than explain such terms as hysterosalpingogram, necropsy or hermaphrodite which are hardly vital to the understanding and interpretation of vaginal smears.

Erica Wachtel

"Modern Trends in Pathology." Edited by DOUGLAS H. COLLINS. Pp. 334, with 135 illustrations. Butterworth & Co., Ltd., London, 1959.

THIS volume consists of a series of essays in Pathology. The author has gathered a team of 14 contributors to write chapters on those subjects on which they are experts. Naturally the chapters vary widely in style and treatment but it can be fairly said that each is an authoritative statement of the subject chosen. If we pick only certain chapters for mention it is solely because they are likely to be of special interest to our readers; every chapter is of interest to the pathologist but not all are of equal interest to the clinician. Dr. R. H. Mole has written a valuable account of the effects of whole body irradiation. This can be recommended to everyone

who uses irradiation therapeutically and who wants to know the effects of radiation on the whole patient as well as on the diseased tissue. Professor R. A. Willis has written an admirable chapter in his inimitable style on a group of uncommon and recently recognized tumours. Though only a few are in the realm of gynaecology the whole chapter is interesting to the general surgeon and Professor Willis is always worth reading. Professor J. N. P. Davies' chapter on cancer in Africa explodes a number of old myths about cancer in primitive peoples and gives much interesting data on the relative frequencies of different tumours in Africans and Europeans. This work holds promise of a better understanding of environmental factors in the genesis of cancer. Dr. W. W. Park's chapter on disorders arising from the trophoblast is of special interest. He deals with the origin, behaviour and diagnosis of hydatid mole, chorion epithelioma and so-called syncytial endometritis. He discusses the recent interesting observations on the sex chromatin in these lesions. He also deals with non-neoplastic trophoblastic pulmonary embolism, with the problem of trophoblast in teratomas and the relationship of the trophoblast to the toxaemias of pregnancy. Professor A. C. P. Campbell gives an admirable account of the pathological relationships of 5-hydroxytryptamine in all its aspects and offers a suggestion that this substance may play a part in the genesis of symmetrical cortical necrosis of the kidney. Readers will welcome the chapter by Professor T. Symington on the human adrenal cortex. Those who have not read his original papers—and many who have—will be grateful for this excellent review of the whole subject of adrenal cortical activity. Finally the editor himself has written an excellent account on pathological ossification and osseous metaplasia. This chapter fills a real need by dealing with aspects of bone pathology that are so poorly understood even by pathologists. The other chapters by Sir Roy Cameron, Professor R. J. V. Pulvertaft, Professor Murray Angevine, Professor C. L. Oakley, Dr. W. G. Spector, Professor P. E. Steiner, Professor G. Payling Wright and Professor J. Gough are no less interesting or valuable than those reviewed above. It is true to say that we enjoyed and learned from all of them. To the pathologist this book is warmly recommended and to the clinician we would say that there is good value for 70s. even if he only reads a half. The production and illustrations are good.

C. V. Harrison

"Cesarean Section"—Edited by E. J. De Costa, and "Advances in Gynecologic Surgery"—Edited by S. B. Gusberg. *Clinical Obstetrics and Gynecology*. Vol. 2, No. 4 (December, 1959). Hoeber, New York, 1959. Price $18 per year.

Clinical Obstetrics and Gynecology is a quarterly publication in book form, each number of which contains symposiums on two subjects with about 10 papers or essays devoted to each of the selected topics. This eighth number deals with Caesarean section and advances in gynaecological surgery, and all the authors are from the U.S.A. In the first symposium little diversity of opinion is manifest, and in particular "once a Caesarean, always a Caesarean" seems generally accepted and practised. Perhaps the most interesting paper is that by Dr. H. C. Hesseltine in which he shows that abdominal delivery, even in favourable cases free from any complications, carries a worse prognosis for the foetus than does vaginal delivery.

The second symposium is more interesting because it ranges over a wider field. There is a stimulating discussion by Dr. R. B. Scott of the pain of endometriosis, and in advocating conservative surgery he coins a memorable epigram—that to any woman a part of an ovary is worth a bushel of hormones. Perhaps the outstanding paper in the gynaecological section is the relatively lengthy account of pelvic exenteration from the authoritative pen of Dr. Langdon Parsons.

REVIEW OF CURRENT LITERATURE

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ANATOMY

132. **The Sexual Response Cycle of the Human Female. I. Gross Anatomic Considerations.**

By W. H. MASTERS. *West. J. Surg. Obstet. Gynec.*, **68**, 57–72, Jan.–Feb. 1960. 7 figs. 46 refs.

This is the first of a number of papers coming from the Sex Research Project at Washington University School of Medicine. The sexual response cycle is divided into four arbitrary phases: (1) the excitement phase, (2) the plateau phase, (3) the orgasmic phase, and (4) the resolution phase. By reviewing literature and the use of coloured cinematography all aspects of the female anatomy during sexual excitement are described in detail. Previously undescribed phenomena include the marked vascular flush which affects some individuals and which may resemble measles and the vivid colour changes which take place in the labia minora. Contrary to previous beliefs, the Bartholin glands do little to lubricate the vagina, a "sweating-phenomenon" of the vaginal walls themselves being the chief mechanism. The anatomical reaction is primarily vasocongestive in nature and this response is not confined to the primary or secondary sex organs; irresolution of this vasocongestion may result in genital pain of various types.

[This is a very long and very detailed paper which is quite impossible to abstract. No practical details of the investigation are given and a valid criticism is one which was levelled at the "Kinsey" reports, all that is described may be true for the individuals described but there is not a shred of evidence that it applies to the population in general.]

D. C. A. Bevis

133. **Pelvic Phlebography.**

By S. P. WEGRYN and R. A. HARRON. *Obstet. and Gynec.*, **15**, 73–79, Jan. 1960. 12 figs. 13 refs.

Pelvic phlebography is the gross radiological observation of pelvic veins by means of radiopaque medium. The technique consists of inserting a cannula through the cervix up to the fundus uteri. A long needle is passed through the cannula, 3 mm. longer than the cannula, and 20 ml. of 50 per cent Hypaque with hyaluronidase is injected into the myometrium. Other techniques included injecting the myometrium at the time of laparotomy and injecting the fluid into the cervix.

The results of investigating 50 cases show that venous drainage in the non-pregnant female from the uterine fundus is via the uterine and ovarian pedicles. From the anterior cervical lip it also drains via the sacral plexus. From the posterior cervical lip it drains via the uterine pedicles. Venous drainage from the uterine fundus immediately post-partum is via the ovarian pedicles alone.

Collateral circulation after ligation of the vena cava and ovarian veins is principally via the perivertebral and

azygous systems. This may occur in a normal female when she strains and thus offers a possible route of metastasis.

J. G. Dumoulin

134. **The Developmental Anatomy of the Cervix Uteri.**
By C. F. Fluhmann. *Obstet. and Gynec.*, **15**, 62–69, Jan. 1960. 8 figs. 21 refs.

The mucosa of the foetal cervix during the last three months of pregnancy presents characteristic changes in its secretory and growth activity, which are distinct from those of the corpus uteri. There are two possibilities to explain this difference.

The first is that this small portion of the mesodermal Müllerian duct will respond to maternal hormones, while the adjacent corporal portion will not do so at this stage. The second is that the cervical epithelium is of entodermal (urogenital sinus) origin. The staining reactions, the enhanced cellular activity, and the inherent property of developing squamous prosoplasia (metaplasia), which are characteristic of other sinus derivatives, speak in favour of this second concept.

J. G. Dumoulin

PREGNANCY

135. **Trophoblast in the Circulating Blood During Pregnancy.**
By G. W. Douglas, I. Thomas, M. Carr, N. M. Cullen and R. Morris. *Amer. J. Obstet. Gynec.*, **78**, 960–969, Nov. 1959. 11 figs. 12 refs.

Various workers have demonstrated trophoblast in the lungs in fatal cases of eclampsia, but the possibility that this was a terminal event and due to manipulation or convulsions has never been excluded. The present authors took blood at Caesarean section at various stages of pregnancy from the placental site by puncture of the uterine wall, and from broad ligament, ovarian, uterine and antecubital veins, as well as from the inferior vena cava. Blood from the broad ligament veins contained trophoblast in 8 of 13 cases. Trophoblast was much more frequent in the second trimester, and in a pregnancy terminated at 18 weeks there was at least one cell per ml. of blood in the venous return from the uterus. Samples of peripheral blood from the antecubital vein of 80 patients were all negative. Trophoblast was difficult to find in blood from the inferior vena cava and was only demonstrated in 3 of 33 cases, some of which were in active labour.

It is suggested that the tolerance of the mother for the foetal homograft which is, of course, genetically different from the maternal host, may be due to transportation of trophoblast, as it has been found that tolerance to homografts can be induced in animals by previous injection of the donor's cells.

F. J. Browne

136. **Measurement of Uterine Blood Flow and Uterine Metabolism. VII. Uterine and Fetal Blood Flow and Oxygen Consumption in Early Human Pregnancy.**
By N. S. Assali, I. Rauramo and T. Peltonen. *Amer. J. Obstet. Gynec.*, **79**, 86–98, Jan. 1960. 2 tables. 8 figs. 29 refs.

This study was carried out on 12 patients who underwent therapeutic abortion by hysterotomy between the 9th and 28th week of gestation. The data obtained show that up to the end of the 28th week the uterine blood flow increases progressively with the increase in gestational age and growth of the ovum. Probably because of the increasing uterine blood flow oxygen consumption by the uterus also increased as pregnancy progressed.

F. J. Browne

137. **An Immunologic Characteristic of the Serum of Normal Pregnancy.**
By J. A. MacLaren, R. D. Thornes, C. C. Roby and D. E. Reid. *Amer. J. Obstet. Gynec.*, **78**, 939–945, Nov. 1959. 6 figs. 8 refs.

There have been various attempts to demonstrate an allergic reaction in pregnancy, notably that by Kaku in 1953 who demonstrated the presence of a polysaccharide with antibody formation in fatal cases of toxaemia. The present paper claims to have proved the presence in normal pregnancy serum of one or two antigenic substances which are neither chorionic gonadotrophins nor isoagglutinins against blood groups A or B. Their significance remains to be established. *F. J. Browne*

138. **Medical Research Council, Obstetrical Research Committee Report on Eclampsia, 1956–58.**
By T. F. Corkill. *N.Z. med. J.*, **58**, 798–800, Dec. 1959. 5 tables.

This report on the last three-year period 1956–1958 shows that the encouraging trends with regard to eclampsia have been maintained. The incidence has fallen from 3·2 per thousand 30 years ago to 1·25 per thousand in 1953–1955, and now to 0·08 per thousand in this period under review. There were five maternal deaths, and this represented a maternal mortality of 3·5 per cent. Infant deaths numbered 29 in 154 (including 12 twins), a mortality of 18·8 per cent. Very mild cases again predominated; these cases were those in which the mother and infant survived, and there were three or less fits. There were 87 of these cases, or 61 per cent. Thirty per cent of cases occurred ante-partum, 33 per cent intra-partum and 37 per cent post-partum. The incidence of Caesarean section continues to decline, there being only 11 such operations in the three years under review.

L. Woodrow Cox

139. **Permanent Renal Lesions after Severe Pre-Eclampsia and Eclampsia.**
By L. Rauramo, A. Kasanen, O. Castren and A. Salmi. *Acta obstet. gynec. scand.*, **38**, 670–680, 1959. 7 figs. 6 refs.

During the years 1951–1957, 244 cases of severe pre-eclamptic toxaemia and 48 cases of eclampsia (2·58 per cent and 0·51 per cent respectively of all deliveries) were

treated at the obstetric department of Turku (Finland) University Hospital. One hundred and fifty-six and 26, respectively, of these were examined one to seven years after delivery. Their renal function was tested by phenolsulphonphthalein and creatinine clearance tests. The blood pressure, urine, ocular fundi, and haemoglobin levels were also examined, and in appropriate cases, intravenous pyelography was done.

Permanent renal lesions, possibly caused by toxaemia, were found in 7 per cent of the cases examined. Pyelonephritis was shown to be just as frequent in normal controls (5 per cent) as in those who suffered from toxaemia.

[This is an important problem. Unfortunately this study is marred by (*i*) presupposing that there were no instances of previous impairment of renal function among the 182 patients followed up, and (*ii*) by the fact that 38 per cent of the patients originally treated did not attend the follow-up; some of these may have, or have died from, renal disease.] *N. Alders*

140. **Chorionic Gonadotropin in the Treatment of Repeated Abortion. A Survey of Fifteen Years Clinical Experience.**

By D. W. DECARLE and R. E. KREISS. *West. J. Surg. Obstet. Gynec.*, **67**, 344–348, Nov.–Dec. 1959. 10 refs.

The authors, from San Francisco, report their results in 124 patients; however, only 42 of these had had 3 or more abortions to justify classification as cases of "repeated abortion". Of these 42, 12 aborted (27·6 per cent) while receiving 5,000 units of chorionic gonadotrophin twice weekly. Four of these patients subsequently went to term with the same treatment and 3 others went to term without any gonadotrophin whatsoever.

The treatment is of no value once bleeding or pain has occurred, and larger doses produce no better results. Treatment is expensive, the cost of the preparation being estimated at between 175 and 200 dollars.

D. C. A. Bevis

141. **Modern Management of Placenta Praevia.**

By J. L. WRIGHT. *N.Z. med. J.*, **58**, 560–570, Oct. 1959. 6 tables. 18 refs.

This paper records the results of the Queen Mary Maternity Hospital, the teaching unit of the University of Otago. In 5,549 births there were 73 cases of placenta praevia, an incidence of 1:76. The foetal mortality was 8 (11 per cent), all of the babies lost being premature. There was no maternal mortality. The author discusses the conservative management of placenta praevia, and emphasizes the clinical features which lead to the diagnosis. X-ray examination for the placental site is made after the 34th week. Later, a decision about the method of delivery is made. This decision may be made without vaginal examination, but usually the latter is performed. Delivery was by Caesarean section in 77 per cent of cases, and vaginally, with or without preliminary rupture of the membranes in the remainder. The author attributes the improved foetal results to the increased use of Caesarean section in cases which have reached maturity. *L. Woodrow Cox*

142. **Some Considerations on the Role of Endometriosis in the Aetiology of Extra-Uterine Pregnancy in General and of Tubal Pregnancy in Particular.** (Considérations sur la place de l'endométriose dans l'étiopathogénie de la grossesse extra-utérine en général et spécialement de la grossesse tubaire.)

By C. STANCA, M. JONESCO, D. L. RATZIOU and J. ANGHEL. *Gynéc. prat.*, **10**, 237–250, 1959. 22 refs.

The authors have been impressed by the fact that out of 8 cases of tubal pregnancy removed by them, 6 have been found on detailed histological examination to show islets of endometriosis near the site of the pregnancy. They suggest that enough attention has not been paid to endometriosis as an aetiological factor of extra-uterine pregnancy. It is, they feel, far more important, as a predisposing lesion than partial tubal blockage and tubal damage. They consider the occasional presence of a haemato-salpinx in the contralateral tube at the time of laparotomy for a tubal ectopic as sure evidence of tubal endometriosis, and that such a tube should be removed. They observe that this possibility that tubal endometriosis favours tubal pregnancy raises a problem when endometriosis is encountered at laparotomy; a problem which they say is solved by those who regard the condition as indication for castration.

[Gynaecologists working in countries where pelvic inflammatory disease and ectopic gestation are remarkably common and endometriosis rare will have difficulty in accepting the views on the aetiology of tubal ectopics expressed by these authors, quite apart from the radical treatment of endometriosis to which they give prominence but do not specifically advocate.] *Geoffrey Dixon*

LABOUR

143. **The Action of the Autonomic System during Labour.** (Vegetative Regulationen unter der Geburt.)

By C.-J. RUCK. *Zbl. Gynäk.*, **81**, 1889–1899, Nov. 28, 1959. 11 figs. 2 tables. 36 refs.

The author attempted to assess the effects of the sympathetic and parasympathetic nervous systems in labour by determination of the serum calcium and potassium levels and the K/Ca quotient in 364 cases. In patients who were in the first stage of labour, uterine contractions were measured with external tocography. The quotient averaged 1·87 before and 1·84 after rupture of the membranes, and remained practically constant during the first stage of labour, irrespective of the quality of uterine contractions. There was a regular drop to an average of 1·75 during the second stage of labour.

It is claimed that relaxation of the cervix rather than the quality of uterine contractions depends on the influence of the autonomic nervous system. A high K/Ca

quotient in spite of strong uterine contractions in cases of colicky inertia denotes predominance of the sympathetic and consequent delay in labour.

The decrease in the quotient during the second stage of labour is attributed to increased "tone" of the parasympathetic.

Bruce Eton

144. **Physiology and Pathology of the Uterus in Labour.** (Physiologie und Pathologie des gebärenden Uterus.)

By R. BAYER. *Zbl. Gynäk.*, **82**, 241–263, Feb. 13, 1960. 20 figs. 6 tables. 101 refs.

This is a digest of modern views on the anatomy and physiology of the uterus in normal and abnormal labour. An account is given of the changes in the uterine muscle during pregnancy, including the chemical and electrobiological processes and the anatomy and function of the uterine nerve supply. The author deals with the structural changes, particularly those occurring in the uterine muscle fibres in pregnancy and labour, the difference in innervation of the various parts of the uterus, the shift of contractile dominance from the cervix to the corpus, the pressure changes in the uterine cavity and the mode of cervical dilatation. The pathological anatomy and physiology of the uterus are considered with reference to congenital and acquired anatomical abnormalities (including anterior and posterior displacement of the os). Classifications of abnormal uterine functions in labour and various forms of cervical dystocia are discussed.

Bruce Eton

145. **The Size and Shape of the Pelvic Inlet in Cases of Premature Rupture of the Membranes Associated with Failure of the Presenting Part to Engage.**

By N. E. PÄHLSSON. *Acta obstet. gynec. scand.*, **38**, 661–669, 1959. 1 fig. 5 refs.

During the years 1955–1959 X-ray pelvimetry was done on 918 pregnant women at the Karolinska Hospital in Stockholm. In 230 (25 per cent) of these cases the indication was premature rupture of the membranes associated with failure of the presenting part to engage.

There was no significant abnormality of the size and shape of the pelvic inlet in these cases. As this complication is thus not due to cephalo-pelvic disproportion it is doubtful if routine radiological pelvimetry is necessary in these cases.

N. Alders

146. **Single Application of Intravenous Pitocin for Induction of Labor in Toxemias of Pregnancy.**

By C. FIELDS. *Amer. J. Obstet. Gynec.*, **79**, 180–185, Jan. 1960. 3 tables. 15 refs.

The author achieved vaginal delivery in 45 out of 50 cases with unresponsive toxaemia of pregnancy, including 23 primiparae. In all cases the presenting part was unengaged and the cervix unripe. In the primiparae the cervix was long and closed, and though the multiparous cervices were often patulous, the internal os was closed; 21 of the 45 vaginal deliveries were premature. There was only one foetus whose death was attributed to the pitocin. It presented by the breech and weighed 2 pounds 10 ounces.

The pitocin was given by intravenous drip in 5 per cent dextrose. Massive doses were not generally employed or needed. One ampoule per 1,000 ml. of 5 per cent dextrose in water was used initially. The flow began at 15 drops per minute, and was gradually increased according to the uterine response. The majority of patients responded to a rate of between 40 and 60 per minute. If an adequate response was not obtained with one ampoule per 1,000 ml. of fluid given at a maximum rate of 80 drops a minute, it was not usually got with larger doses.

F. J. Browne

147. **Relaxin.**

By S. L. ISRAEL and W. R. GROEBER. *Obstet. and Gynec.*, **15**, 2–8, Jan. 1960. 33 refs.

Relaxin, which is produced from the corpora lutea of pregnant sows, softens the symphysis pubis in some animals, in which it seems essential to parturition. It has been identified in the blood serum of pregnant women and it is thought to originate in the placenta, although only very small amounts have ever been found in that organ. It has not been found in the human ovary, myometrium or amniotic fluid. It is a mixture of several unidentified polypeptides of low molecular weight, and is inactive if taken orally. It is not antigenic and its injection produces no side effects.

Relaxin inhibits myometrial contractility in the human non-pregnant uterus. On this basis, it has been recommended for dysmenorrhoea and threatened premature labour. Shown to soften the cervix in animals, it has been used to shorten labour and to ripen the human cervix. Relaxin certainly has no inhibiting effect upon labour after the thirty-fourth week. It is obvious that additional controlled observations are needed before a proper judgment can be given of its clinical uses. Present therapeutic experiments with relaxin are hampered by lack of precision.

J. G. Dumoulin

148. **The Practical Value of the Oxytocin Sensitivity Test.** (Der praktische Wert des Oxytocin-Sensitivity-Testes.)

By H. HUSSLEIN, K. BAUMGARTEN and W. HOSHANGL. *Zbl. Gynäk.*, **82**, 49–57, Jan. 9, 1960. 7 figs. 7 refs.

Obstetricians frequently have to decide whether to carry out induction of labour in cases of prolonged pregnancy, toxaemia or uncertainty of the expected date of delivery. By means of the oxytocin sensitivity test it is possible to foretell whether the uterus will readily go into labour once the membranes have been ruptured artificially.

The procedure was as follows: prior to the test the patient rested comfortably for 15 minutes. A solution of 0·01 units of syntocinon per ml. of saline was injected intravenously at the rate of 1 ml. per minute up to a maximum of 5 ml. The amount required to produce the first registrable uterine contraction was noted.

In 182 patients the contraction was recorded tocographically and in 172 by simple palpation. There was no significant difference in the findings by the two methods. In order to reduce the possibility of error caused by spontaneous uterine contractions the test was repeated on two successive days. In 52 patients the test was followed by artificial rupture of the membranes.

As the two methods of recording yielded no significant difference, the authors point out that tocography is not essential for the test.

It was found that following a positive reaction with 2 ml. (0·02 units) labour was very likely to start within 48 hours. Such a forecast could not be made if 0·03 units or more were required.

In their series of 58 patients whose membranes were ruptured if the test was positive with 0·01 to 0·02 units, 77 per cent were delivered within one day, and 97 per cent within 48 hours.

The authors conclude that the test introduced by Smyth (Smyth, C. N., *Triangle: Sandoz J. med. Sci.*, 1957, **4**, BIII) provides a useful practical means of forecasting the response of the uterus to artificial rupture of the membranes.

Bruce Eton

149. **Studies of Oxytocic, Relaxing and Haemodynamic Agents in the Liquor Amnii.** (Untersuchungen über die oxytozischen und relaxierenden Prinzipien sowie kardiovaskulären Faktoren des Fruchtwassers.)

By B. CUPARENCU, E. T. BIRSAN, V. IDU, L. GROSU and L. TOMUS. *Zbl. Gynäk.*, **82**, 192–198, Jan. 30, 1960. 6 figs. 7 refs.

Amniotic fluid was obtained from 60 women by puncture of the membranes or by direct aspiration in the course of Caesarean section. An extract was prepared which was free of protein and diuretic substances.

Studies *in vitro* and in experimental animals showed that liquor amnii has a definite oxytocic action which is not due to acetylcholine, adrenaline, noradrenaline, adenosine compounds, histamine or serotonin.

In the isolated rabbit heart the extract produces a marked bradycardia which persists in spite of atropine. In cats and dogs under chloralose anaesthesia intravenous injection of the extract causes severe hypotension and apnoea. In some cases, however, prolonged hypertension results. Neither change in blood pressure can be influenced by atropine.

A factor causing relaxation of the uterus was demonstrated towards the end of pregnancy in low concentration, as it could only be detected in highly concentrated extracts.

The authors claim that their observations indicate that the liquor amnii has not merely a mechanical action but also other biological functions, depending on the presence of oxytocic and relaxing factors.

Bruce Eton

150. **Treatment of Threatened Premature Labor with Large Doses of Progesterone.**

By F. FUCHS and G. STAKEMANN. *Amer. J. Obstet. Gynec.*, **79**, 172–176, Jan. 1960. 9 tables. 14 refs.

Sixty-three patients with symptoms of threatened premature labour were treated with progesterone in oil. The dose was 200 mg. given parenterally for three days, 150 mg. for two days and then 100 mg. daily till a week after symptoms subsided. An equal number of controls received the same amount of oil but without progesterone. In both series there was good agreement as regards obstetric history, symptoms, and age, and in both the stage of gestation varied from the 5th to the 9th month, the majority being at the 8th month. The number of patients in whom pregnancy continued to term was the same in both groups. There was no evidence of masculinization in any of the female infants. It is concluded that progesterone is unable to prevent premature delivery once clinical symptoms are present.

F. J. Browne

151. **Experiences with Active Management of the Third Stage of Labour.** (Erfahrungen mit der aktiven Leitung der Plazentarperiode.)

By J. HARTEL. *Zbl. Gynäk.*, **82**, 129–134, Jan. 23, 1960. 4 figs. 46 refs.

The author reports on a series of 150 patients who received 1 ml. (0·2 mg.) of Methergin intravenously at the time of the birth of the foetal shoulder. The series is compared with an equivalent series of controls managed by the traditional expectant method. The average duration of the third stage was 5 minutes in the series and 16 minutes in the controls. The blood loss averaged 103 ml. in the former and 254 ml. in the latter. Manual removal, exploration of the uterus or curettage were required in 4·7 per cent of the series compared with 8·7 per cent in the controls. Haemoglobin estimations carried out in both groups during the puerperium showed considerably higher levels amongst the patients who had prophylactic Methergin.

Bruce Eton

152. **Experiences with Methergin During Active Management of the Third Stage of Labour.** (Erfahrungen mit Methergin bei der generellen aktiven Leitung der Placentarperiode.)

By D. SCHMITZ-HERTZBERG. *Zbl. Gynäk.*, **82**, 134–140, Jan. 23, 1960. 2 figs. 35 refs.

This is a report on the results of the routine use of Methergin 1 ml. (0·2 mg.) injected intravenously after delivery of the shoulders or immediately following the birth of the child.

The series consisted of 507 patients between the ages of 15 and 44 years. The average blood loss was 140 ml. It was observed that bleeding was more marked if a general anaesthetic was used. There were 5 cases of secondary haemorrhage with a blood loss between 150 and 500 ml. Uterine atony was also observed in 5 patients, occurring in 1 woman after 3 minutes, and in 2 others after one hour. The blood loss ranged from 200 to 800 ml. The average time interval between the birth of a child and the placenta was 1 minute 31 seconds, excluding 4 cases of retained placenta. A second dose of Methergin had to be injected into 5 patients for the treatment of

either uterine atony or incomplete separation of the placenta.

The author considers that retention of the placenta need not cause any alarm. Haemorrhage will not occur. After about 20 to 30 minutes the cervix will relax and the placenta can be expressed.

Methergin did not seem to have any effect on the blood pressure.

Bruce Eton

153. **Automatic Device for Tying the Umbilical Cord.** By L. C. GRAVLEE and W. N. JONES. *Obstet. and Gynec.*, **15,** 43–46, Jan. 1960. 3 figs. 8 refs.

The authors have devised an automatic metal loader which places a piece of latex rubber tubing around a loop of umbilical cord. This acts as an efficient ligature. The loader can be fitted with 10–15 latex bands and is sterilized by soaking in Zephiran (benzalkonium chloride) 1:1,000 solution for at least 24 hours.

Of the 2,663 cases on which the gun tie was used, only one stump bled, and that not severely. There appeared to be a reduced neonatal stump infection compared with the conventional cotton tape tie.

J. G. Dumoulin

LACTATION

154. **Lactagogue Action of Oxytocin.** (Oxytozin als laktagoges Hormon.)

By C. HOLLENBACH. *Zbl. Gynäk.*, **81,** 1980–1986, Dec. 12, 1959. 1 fig. 3 tables. 51 refs.

Whenever a mother puts her infant to the breast there is a reflex outflow of oxytocin from the neuro-hypophysis, which is responsible for the "letting down" of the milk. The milk ejection is due to contraction of the myo-epithelial cells surrounding the alveoli. The afferent limb of this reflex is nervous, but the efferent is humoral. It is well known that this reflex can easily be linked to other environmental influences and thereby become a conditioned reflex.

The author investigated the effects of synthetic oxytocin ("Syntocinon") as a nasal spray in 351 patients, and found that it is as effective as parenteral injection. Whenever a patient required this "milk ejection hormone" a unilateral nasal spray was applied before a feed was due. It was estimated that by compressing the vaporizer for 1 second about 4–5 units were administered. The indications were: breast engorgement in 118 patients; stagnation of milk in cases where the child failed to empty the breast because of weakness or prematurity in 179 patients; early mastitis in 18 patients; inadequate lactation from the 4th day in 36 patients.

It was found that oxytocin helped to relieve painful tension due to engorgement of the breast; it diminished the trauma to the nipple by reducing the duration of the feed; it reduced within 24 hours the painful swelling of the axillary tail; expression was easier in cases in which the child was unable to empty the breast; the complete emptying of the breast encouraged an increase in milk yield.

Bruce Eton

155. **Suppression of Lactation with Largactil in Experimental Animals.** (Tierexperimentelle Untersuchungen zur Laktationshemmung mit Largactil.)

By G. FARKAS and I. NEGRUT. *Zbl. Gynäk.*, **81,** 1987–1992, Dec. 12, 1959. 7 figs. 21 refs.

Inhibition of lactation by oestrogens is believed to act via the hypophysis which stimulates the ovaries and suprarenals to produce an excess of progesterone. This, in turn, suppresses the secretion of milk.

In a series of pregnant albino rats with controls Largactil was given partly before and partly after the onset of lactation. Histological examination of the mammary glands showed regression of the acini which were closely packed, with narrow lumina. The cells of the alveolar epithelium did not show any secretory changes. Inhibition of lactation was achieved irrespective of whether Largactil was given before or after its onset.

Largactil is believed to interrupt the pathways between the higher centres of the brain, the hypothalamus and the hypophysis.

Bruce Eton

156. **Novobiocin and Prednisolone in Puerperal Mastitis.** By F. R. OLAVE, J. J. FERNANDEZ and J. A. LACADENA. *Obstet. and Gynec.*, **14,** 806–810, Dec. 1959. 2 tables. 29 refs.

Twenty-one cases of puerperal mastitis were treated with novobiocin and prednisolone. It is frequently found that penicillin, streptomycin and tetracycline are ineffective in this condition, which is usually due to infection by *Staphylococcus aureus*. Erythromycin and chloramphenicol are sometimes effective, but antibiotic sensitivity tests demonstrate that novobiocin is effective.

In puerperal mastitis there is usually an intense inflammatory reaction with abscess formation for which reason it would seem helpful to use an anti-inflammatory agent.

Thirteen early cases of mastitis were treated and 8 late ones. One gramme of novobiocin was given daily together with 20 mg. of prednisolone, the dose being reduced when fever and erythema disappeared. The treatment was promptly effective, and none of the early treated cases had suppuration.

J. G. Dumoulin

INFANT

157. **The Effects of Pregnancy and Labour on the Respiratory Pattern of the Newborn Infant: Subsequent Morbidity and Mortality.**

By L. A. CALKINS and H. C. MILLER. *Amer. J. Obstet. Gynec.*, **78,** 1005–1009, Nov. 1959. 4 tables. 1 fig. 6 refs.

The authors state that in newborn infants whether premature or full time, excluding those with gross congenital abnormalities, a highly accurate prognosis regarding survival can be given by observing the breathing pattern after birth. If this is normal the baby is likely to survive; if it is not the baby may only survive if it receives special care. The causes of this abnormal pattern seemed to be: premature rupture of membranes (more than 24

hours before onset of labour), toxaemia including eclampsia, and moderate or severe asphyxia neonatorum. Analgesics or anaesthetics did not seem to cause it, but it was twice as frequent after Caesarean section as after vaginal delivery, even after making allowance for the abnormality which made the Caesarean section necessary.

F. J. Browne

158. **Birth Injuries and Malformations and Their Treatment.** (Lesioni da parto e malformazioni del neonato: indicazioni all'attuazione di trattamenti terapeutici.)

Minerva ginec. (*Torino*), **23**, 995–1004, Dec. 15, 1959. 5 tables. 11 figs. 16 refs.

At the University Clinic of Turin from 1950 to 1958 there were 105 cases of birth injury among 15,724 births, a percentage of 0·66, but it is notable that in the last two of these years the percentage fell to 0·23. *Fractured clavicle*, partial or complete, occurred 53 times, and whilst all cases recovered completely whether treated or not, where there is separation of the fragments it is recommended that extension by bandage or plaster is desirable for up to a week in view of others having reported occasional cases of non-union. *Paralysis of the brachial plexus* of the Erb-Duchenne type was met with 16 times and calls for immediate recognition if permanent damage is to be avoided. The arm and shoulder must be maintained by a plaster splint in the position of the balancing arm of an epée fencer though due regard may have to be paid to respiratory difficulties of independent origin (atelectasis, etc.). Under this treatment all cases recovered satisfactorily except one which had escaped early detection. In such cases and in *facial paralysis* due to forceps pressure vitamin B is given, and in the latter special feeding difficulties may have to be overcome in the first few days of life. *Fractures* of the humerus and of the femur are usually the result of difficulties in breech extraction. The arm is held by plaster in abduction with elbow flexed and forearm in half supination. For the thigh, extension is applied but full reduction is not usually obtained; nevertheless the end result is excellent. Callus is deposited in the newborn with remarkable rapidity. Extra calcium may be given to ensure this. *Cephalhaematoma:* an expectant line is advocated because early evacuation often leads to fresh bleeding. Vitamins C and K are used and if absorption is unduly prolonged aspiration may be undertaken at the end of a week. *Intra-cranial haemorrhages:* the diagnosis from the effects of asphyxia may be difficult. Haemostatics, sedatives and other symptomatic treatment may be given, but treatment is unsatisfactory and prognosis pessimistic.

There were 115 cases of malformations, a percentage of 0·73. The chief numerically were hypospadias, harelip and cleft palate, and talipes. The duty of the obstetrician is their early recognition, both to save life (as in imperforate anus) and to correct deformities with the help of the paediatrician and orthopaedist and general surgeon. Congenital hip dislocation can be suspected where the legs lie everted or where the inguinal or gluteal skin folds are asymmetrical. Early orthopaedic treatment gave splendid results.

Of the total neonatal mortality figures for the Clinic, 7 per cent were attributable to birth injury and 23 per cent to foetal malformations. *W. C. Spackman*

159. **Fetal Death Before the Onset of Labor. An Analysis of 407 Cases.**

By D. J. GRANDIN. *Amer. J. Obstet. Gynec.*, **79**, 237–243, Jan. 1960. 6 tables. 7 refs.

The incidence of foetal death before the onset of labour, including all foetuses exceeding 500 g. in weight was 1·2 per cent. The death was unexplained in 113 (28 per cent); toxaemia was the cause in 26 per cent, abruptio placentae in 14 per cent, erythroblastosis in 9 per cent, obstructed cord circulation in 7 per cent, diabetes and sickle cell anaemia in 3 per cent, external version in 0·7 per cent, amnionitis and congenital pneumonia in 1 per cent, congenital abnormalities in 11 per cent, "postmaturity" in 0·7 per cent (3 cases). Foetal death occurred after the end of the 41st week in 16 but only in these 3 was there no other contributing factor discovered to account for the death. It is, however, relevant to note that before the 42nd week there were 113 unexplained deaths for which no cause could be found.

Post-partum haemorrhage occurred in 6 per cent as compared with an incidence of 3 per cent in the whole service, and transfusion was given to 20 patients. In 9 it was necessitated by haemorrhage from abruptio placentae or placenta praevia. Two of the others were transfused at Caesarean section and one for a sulcus tear. Only one case of hypofibrinogenaemia was discovered, and was corrected by 2 mg. fibrinogen. Though most of the series of foetal deaths occurred before afibrinogenaemia was popularized, these data suggest that hypofibrinogenaemia may be, if not rarer, at least far less dangerous than some of the recent literature would suggest. The importance of both postmaturity and hypofibrinogenaemia in cases of foetal death before the onset of labour is questioned. *F. J. Browne*

160. **Stillbirth and Ways to Reduce It.**

By V. A. KUSNETSOV and A. B. SIGALOV. *Amer. J. Obstet. Gynec.*, **79**, 244–248, Feb. 1960. 3 tables. 3 refs.

This is a study of 810 stillbirths in the obstetrical institutions of Stalinskaya, U.S.S.R. Antenatal death occurred in 30 per cent and intranatal death in 70 per cent. The deaths are divided into 4 groups according to whether they are due to maternal, foetal, placental or indeterminate causes. Among the maternal causes prolonged dry labour was far the most frequent, accounting for 15 per cent of all stillbirths. The application of the Verloft binder which shortens labour and relieves pain, especially in the second stage when the abdominal wall is defective, is advocated, as well as frequent auscultation of foetal heart sounds—every 10–15 minutes in the first stage, and every 3 to 5 minutes in the second. The chief foetal causes of stillbirth were breech presentation and

twin pregnancy. The greater risk to the second twin is emphasized and its active delivery without much delay is advised. Placental causes include placenta praevia and coiling of the cord. For the former earlier hospitalization is advocated, and version when the os is incompletely dilated condemned. In marginal placenta praevia the scalp forceps of Ivanov considerably reduces the stillbirth rate and often controls haemorrhage. The qualifications of obstetrician-gynaecologists should be raised, and they should be sent periodically to study the causes of stillbirth in the lying-in hospitals. The raising of the qualifications of midwives is also obligatory. The main difficulty in the study of stillbirths is the high percentage of indeterminate causes (26 per cent in this series), for the elimination of which careful documentation of the management of labour and autopsy of all stillborn infants should be made routine—including examination of placenta and cord.

F. J. Browne

OBSTETRIC OPERATIONS

161. **Perinatal Mortality in Primary Cesarean Section.**
By P. PEDOWITZ, R. M. SCHWARTZ and M. GOLDBERG. *Obstet. and Gynec.*, **14**, 764–772, Dec. 1959. 11 tables. 16 refs.

Perinatal Mortality in Repeat Cesarean Section.
By R. M. SCHWARTZ, P. PEDOWITZ and M. GOLDBERG. *Obstet. and Gynec.*, **14**, 773–779, Dec. 1959. 8 tables. 13 refs.

In these 2 papers the perinatal mortality was assessed in 1,433 primary and repeat Caesarean sections done between 1953 and 1957 at the Jewish Hospital of Brooklyn. There were 853 primary sections, an incidence of 3·7 per cent, 861 babies being delivered of which 38 were lost—a perinatal mortality of 4·4 per cent. It was estimated that 37 per cent of this total foetal loss was not related to the mode of delivery, since the deaths occurred prior to the Caesarean section. When this fact is coupled with the number of preventable neonatal deaths, it is estimated that the foetal risk inherent in Caesarean section is less than 0·2 per cent, because not one death in the series could be attributed to the mode of delivery. In fact, Caesarean section improves the overall foetal salvage.

The incidence of repeat Caesarean section was 2·5 per cent with a perinatal mortality of 3·1 per cent. Errors in obstetric judgment, particularly in producing premature babies, are important factors in the production of foetal wastage, and it is therefore best to await labour before doing a repeat section. Only 3 foetal deaths were attributable directly to repeat section, and 2 of these were due to errors in obstetric judgment.

The maternal mortality in the series was one—0·07 per cent.

J. G. Dumoulin

162. **The Fate of the Postcesarean Uterus.**
By J. C. WEED. *Obstet. and Gynec.*, **14**, 780–785, Dec. 1959. 8 tables. 8 refs.

Of 403 patients who had undergone Caesarean section from 1–16 years previously, 35 (14·1 per cent) of those followed had hysterectomy performed. In those followed for 8 years or more the incidence was 29 (27 per cent).

Disturbances of menstrual function were common, often resulting in diagnostic curettage but ultimately in hysterectomy. The author suggests that adenomyosis may follow classical Caesarean section, another reason for preferring the lower segment operation.

When sterilization is desired after repeat Caesarean sections, Caesarean hysterectomy should be considered.

J. G. Dumoulin

GYNAECOLOGY

163. **Gynäkologische Orthopädie.** (Gynaecological orthopaedics.)
By H. MARTIUS. *Acta obstet. gynec. scand.*, **38**, 555–563, 1959.

The basis of this paper by the doyen of German gynaecologists is that the female has to sacrifice some of her locomotor stability to the physiological demands of childbearing.

Changes in the locomotor system must be excluded when analyzing symptoms which may also be caused by abnormalities of the pelvic organs.

N. Alders

164. **Congenital Anomalies of the Uterus.**
By M. THOMAS and I. I. LANGLEY. *West. J. Surg. Obstet. Gynec.*, **67**, 339–343, Nov.–Dec. 1959. 3 figs. 12 refs.

The authors consider 68 patients admitted during 6 years with various abnormalities of the uterus; 45 of the patients were pregnant. A total of 143 pregnancies occurred, resulting in 84 full-term babies, 51 abortions (incidence of 35 per cent compared with normal 5·5 per cent) and 3 ectopic pregnancies. Out of 92 pregnancies, 13 terminated in Caesarean section, an incidence of 14·1 per cent compared with 5·3 per cent for the obstetric service.

The commonest lesions were uterus bicornis (32), uterus didelphys (15) and uterus septus (7). The commonest gynaecological symptom was bleeding (13), and breech presentation was the commonest obstetrical abnormality (13 cases).

D. C. A. Bevis

FUNCTIONAL DISORDERS

165. **The Effect of Psychic and Painful Stimuli on the Reproductive Organs of the Female Rat.**
By K. SOIVA, M. GRÖNROOS, U. K. RINNE and E. NÄÄTÄNEN. *Acta obstet. gynec. scand.*, **38**, Suppl. 4, 1959. 22 pp. 5 figs. 21 refs.

This study, from the University of Turku, Finland,

describes the effects of psychological and painful stimuli on the reproductive system (hypophysis, ovaries, vagina) of the mature female rat; the functional disturbances were compared with organic changes. The psychological stimuli consisted in placing the animal into a very small cage in a dark room, subjecting it to "timed light and sound stimuli", and blowing a strong airstream at it; the painful stimuli consisted in pinching the animal. Each test group of 11 to 12 animals was subjected to this treatment for 1½ hours twice daily, for 2, 14 and 28 days respectively. Each test group had a control group. Vaginal smears were examined, and urine samples were taken for hormone analyses. At the end of the experiment the animals, and their adrenals, hypophyses and ovaries were weighed. In some animals the gonadotrophin content of the hypophysis was estimated, in others the relative number of PAS-positive cells of the hypophysis (which are supposed to be responsible for the production of follicle-stimulating hormone) and the number of primary, Graafian and atretic follicles, and of corpora lutea in the ovaries were determined.

Even after a treatment of 2 days an increase in the size of the adrenals was found, but no changes were observed in the functions and the structure of the organs investigated, with the exception of enlargement and partial degranulation of the PAS-positive cells of the hypophysis, and of ovarian hyperaemia. However, in the animals that had undergone stress treatment for 14 and for 28 days there was a clear and increasing tendency to reduction of the weight of the hypophysis and the ovaries, and to reduction in the size of the PAS-positive cells; the oestrus phases became fewer and finally turned into continuous di-oestrus, corresponding to a proved diminution of gonadotrophic and oestrogenic hormones in the urine.

The authors conclude that the increased gonadal function in acute stress, as well as the decreased function with gonadal atrophy in prolonged stress, are attributable to a change in the production of gonadotrophins by the hypophysis, and are not due to changed sensitivity to gonadotrophin of the reproductive organs.

[The abstracter arrived at similar conclusions (*Z. Geburtsh. Gynäk.*, 1930, **97**, 194) by keeping castrated rodents in a rarefied atmosphere for prolonged periods, and observing the efficacy of injected oestrogens.]

N. Alders

166. **The Effects of Androgenic Steroids on Tertiary Sexual Characteristics.** (Untersuchungen zur Frage der Beeinflussung von tertiären Geschlechtsmerkmalen durch androgen wirksame Steroide.)

By G. Pfeiffer. *Zbl. Gynäk.*, **82**, 220–226, Feb. 6, 1960. 6 figs. 3 tables. 68 refs.

The following are considered to be tertiary sexual characteristics of the female: reduced red cell count, haemoglobin and serum iron levels; increased water content and heart rate; configuration of the nuclear chromatin.

The author set out to investigate whether it was true that nuclear drum-sticks in the leucocytes of the female could not be influenced by androgens. The clinical material consisted of 110 patients who had received post-operative androgen therapy for carcinoma and who had developed virilizing signs after 3 to 30 months of treatment. These women had received between 400 and 1,000 mg. of androgens. There was no statistically significant change in the nuclear sex chromatin. This finding might have been expected but the author felt that it needed to be confirmed, particularly in view of the fact that the sexual characteristics of nuclear chromatin in the blood vary with the maturity and weight of the newborn and the age of the individual.

Bruce Eton

167. **A Comparison of the Effects of Oestriol and Oestradiol.** (Vergleichende Untersuchungen mit dem Östriol und dem Östradiol.)

By A. Puck and W. Komp. *Geburtsh. u. Frauenheilk.*, **20**, 132–141, Feb. 1960. 6 figs. 5 refs.

The authors have previously reported the results of experiments designed to show the actions of oestriol (*Zbl. Gynäk.*, 1958, **80**, 459). The manufacturers have stated that their preparation of oestriol (Ovestin, Organon) is contaminated with 0·4 per cent oestradiol. The authors have therefore performed a further set of blind, controlled experiments. In one group castrated female guinea-pigs were given a total dose of 10 μg., over a period of 20 days, of a specially purified extract of oestriol (the maximum contamination with oestradiol being 0·01 per cent); in another group the animals were given a total dose of 0·04 μg. of oestradiol, i.e., an amount equivalent to the contaminating oestradiol in their previous experiments. A control group was also studied. The animals were killed after 20 days and the genitalia examined histologically. No changes were found in the uteri of any of the animals. But in the cervix and vagina advanced proliferative changes were seen in the animals treated with oestriol. No changes were noted in the oestradiol treated animals compared with the control group.

Peter J. Huntingford

168. **Hypnosis in Gynaecology.** (L'hypnose en gynécologie.)

By V. B. Green-Armytage. *Gynéc. prat.*, **10**, 181–187, 1959.

After tracing the history of hypnosis as applied to medicine back through Shakespeare to the Bible, the author reviews the conditions in which he has found hypnosis valuable. The method he uses is that of Berillon.

In the field of gynaecology he has used this method successfully in the treatment of amenorrhoea, menorrhagia, dyspareunia, dysmenorrhoea and sterility. [The author considers that the success of hypnosis in this last field bears out the French aphorism: "The best cure for infertility is a healthy lodger."] He deals in some detail with hypnosis in obstetrics and prefers it to the current practice of "relaxation" which he suggests is simply a form of auto-hypnosis.

Geoffrey Dixon

169. **The Problem of Functional Dysmenorrhoea.** (Le problème de la dysménorrhée fonctionnelle.)

By P. MEUNIER. *Gynéc. prat.*, **10**, 159–180, 1959.

Functional dysmenorrhoea may be due to any one of a large number of possible causes. Only by very careful history taking and examination can the cause be elicited in each case and appropriate therapy given.

The author groups dysmenorrhoea into obstructive and non-obstructive varieties, and in each group he considers that the pain may be due to functional or organic causes.

He thinks that too much emphasis should not be laid on the psychic element and that it should be possible to relieve almost all cases.

Geoffrey Dixon

170. **Medical Curettage in Menopausal and Post-Menopausal Metropathia.** (Curettage hormonal et métropathie ménopausique et post-ménopausique.)

By PENA-REGIDOR. *Gynéc. prat.*, **10**, 251–253, 1959. 1 ref.

The use of this treatment is acceptable for the young woman, and for the single girl it should be preferred to a dilatation and curettage. This latter need only be undertaken in the event of failure of the medical therapy. In the menopausal and post-menopausal woman the situation is entirely different and hormone therapy should only be used when a curettage has shown the cause of the bleeding to be benign.

In a series of seventy patients with a diagnosis of "menopausal or post-menopausal metropathia" the author detected six examples of adenocarcinoma of the endometrium.

Geoffrey Dixon

171. **Estrogens After the Menopause.**

By W. R. FRAZIER. *West. J. Surg. Obstet. Gynec.*, **67**, 353–358, Nov.–Dec. 1959. 18 refs.

The author examines the literature and recommends that all women without evidence of oestrogen function (diagnosed by vaginal smear) should have oestrogen therapy for the rest of their lives as this prevents osteoporosis, premature arteriosclerosis and senile mental aberrations.

D. C. A. Bevis

172. **Physiopathology and Clinical Signs of Female Sterility.** (Fisiopatologia y clinica de la esterilidad femenina.)

By A. F. MENDIZÁBAL. *Obstet. Ginec. lat.-amer.*, **17**, 355–359, July–Aug. 1959. 15 refs.

In a somewhat detailed account of the interaction of the biochemistry of the various hormones which influence ovulation and conception, the author begins by stating that short phases of amenorrhoea can be due to local action of the sympathetic control of the endometrial blood vessels, but that longer phases are associated with an altered production of luteinizing hormone.

Considerable stress is laid on the relationship between the pituitary gland (anterior lobe) and the hypothalamus, and the role of the latter is illustrated in the case of the rabbit, in which stimulation of the adjacent tuber causes ovulation, even when the pituitary is completely dormant. The posterior lobe of the pituitary is also stated to play a part through its oxytocic hormone, which by causing uterine contractions, enables the spermatozoa to ascend the uterine cavity, since the movement of their tails is no longer thought to propel them. Lack of vitamins and severe malnutrition reduce the production of the gonadotrophins.

Whilst the relationship of the thyroid, the gonads and the suprarenals is not understood, it has been found that if protein-bound iodine does not increase in a pregnancy, abortion follows, but this also depends upon the oestrogen levels. The synthesis of cortisone is liable to fail at the 17-alpha-hydroxy-progesterone stage. Hydrocortisone controls the production of the adrenal corticotrophins, and if any abnormal influence occurs at this stage, the pituitary function is affected resulting in disturbance of the gonadotrophin regulation. In addition, the pituitary balance can be upset by excess of oestrogens or of androgens from the adrenals. Alterations in the thyroid can likewise disturb the endocrine balance, and in the experience of the author, 18 per cent of subfertility is due to this cause, although he mentions that other writers have given estimates varying between 9 per cent and 45 per cent.

In conclusion, the ovaries too are blamed for subfertility either because of atretic follicles, corpus luteum cysts or polycystic disease.

John F. Foulkes

173. **Dysgerminoma and Intersex.** (Disgerminom und Intersexualität.)

By E. PHILIPP and H.-H. STANGE. *Zbl. Gynäk.*, **82**, 9–17, Jan. 2, 1960. 10 figs. 30 refs.

The authors report on two patients from whom a dysgerminoma was removed. Investigation of nuclear chromatin showed that in both cases the patient was female and the tumour male. One patient had normal female characteristics and had been pregnant once. The other, a woman of 19 years, had an enlarged clitoris since birth. Although she developed normal feminine tendencies, her voice had a low pitch. Vagina, uterus and tubes were normal.

Bruce Eton

INFECTIONS OF THE REPRODUCTIVE ORGANS

174. **Occurrence of Trichomonas in Sexual Partners of Women with Trichomoniasis.**

By E. BLOCK. *Acta obstet. gynec. scand.*, **38**, 388–403, 1959. 35 refs.

In a series of cases in which promiscuity was improbable, the sexual partners of women suffering from trichomonas vaginitis were requested to present themselves for medical examination. Ninety-one per cent of the men co-operated, and 91 (61·5 per cent) of the 148 men examined were found to harbour trichomonas vaginalis in their urethra. Seventy-two of the 91 men were completely free from symptoms. That the presence of trichomonas in the urethra of the male is not a transient

phenomenon is apparent from the fact that in 15 of the men the organism was still demonstrable long after the infection in the women had disappeared. *N. Alders*

175. **Is it Wise to Treat a Sterile Woman with Latent Genital Tuberculosis?** (Faut-il traiter une femme stérile atteinte de tuberculose génitale dite "inapparente"?)
By J. E. MARCEL. *Gynéc. prat.*, **10**, 195–205, 1959.

There appears to be sufficient evidence to accept the occasional occurrence of endometrial tuberculosis as an isolated lesion without tubal involvement, although the concurrence of adnexal and endometrial tuberculosis is the rule.

The author reviews the chances of effective cure of pelvic tuberculosis. The rare patient with isolated endometrial tuberculosis has sufficient chance of pregnancy to make the treatment worth while. If, however, pregnancy does follow, the treatment must be repeated to prevent the disaster of miliary tuberculosis especially at the puerperium.

On the other hand, he suggests that tubal tuberculosis is not likely to cause serious illness and that the beneficial results of therapy are dubious. It is almost certain that complete anatomical and functional restoration of the tubes will not occur, and even if pregnancy should be achieved it is almost certain to be tubal.

Balancing this dubious advantage against the expense and inconvenience of treatment he concludes that such treatment should only be carried out at the express desire of the patient and her husband after they have been fully acquainted with the situation.

[This article is an excellent review of the present situation in regard to pelvic tuberculosis. Unfortunately, although many authorities are quoted in the text, there is no list of references.] *Geoffrey Dixon*

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

176. **Chemotherapy for Carcinoma of the Uterus.**
By J. C. BATEMAN, H. N. CARLTON and J. P. THIBEAULT. *Obstet. and Gynec.*, **15**, 35–42, Jan. 1960. 6 tables. 2 figs. 8 refs.

Thirty-nine patients with advanced recurrent carcinoma and two patients with advanced inoperable carcinoma of the uterus were treated with chemotherapy. In 5 patients with incompletely resected carcinoma, chemotherapy was started post-operatively. Thio TEPA (N′, N′, N″—triethylene thiophosphoramide—an agent similar in action to nitrogen mustard) was used in 45 cases. Supplementary therapy was given with Puromycin (puramino) in 7 cases and with Actinomycin D in 3 cases. One patient received the latter drug alone. The treatment was given at 1 to 2 week intervals by the transabdominal or transvaginal route, although in a few cases it was given intravenously or into the pleura.

Maintenance therapy was practical on an out-patient basis. Actinomycin D administration resulted in severe clinical toxicity. Both agents demonstrated haematopoietic effects which could be controlled by individualization of dose according to blood counts.

Thio TEPA appeared to prolong useful survival time in the majority of patients; in some instances this was impressive. Although objective regression of tumour was limited, tumour progression seemed to be slowed. In 2 cases partial regression of pulmonary metastases was demonstrated.

The authors suggest that chemotherapy in early cancer of the uterus may improve survival time and reduce the incidence of late recurrences. *J. G. Dumoulin*

177. **Cytological Cancer Screening: A Simple, Rapid Staining Procedure Applicable to Office Use.**
By A. VARGA. *Obstet. and Gynec.*, **15**, 9–14, Jan. 1960. 6 figs. 9 refs.

The following simple staining technique for vaginal smears has been found to be very effective for office cytology:

(1) Fix the smear in equal parts of 95 per cent alcohol and ether.
(2) Place in full-strength Terry's polychrome methylene blue for 3 to 5 minutes.
(3) Rinse in tap water until clean. Allow excess water to escape by tilting slide edge against absorbent paper.
(4) Put streak of water along one edge with eye dropper and mount the cover slip. Drain off excess water.
(5) Seal edges of cover slip with colourless, rapid-drying nail polish coating.

A disadvantage of this method is the lack of permanency of the stain. *J. G. Dumoulin*

178. **Significance of Performing Dual Smear Examinations in a Mass Screening Survey for Uterine Cancer.**
By Y. S. SONG, H. FANGER and T. H. MURPHY. *Amer. J. Obstet. Gynec.*, **78**, 1309–1311, Dec. 1959. 5 tables. 2 refs.

This is a report of the results of a study of 25,000 women over 20 years of age in Rhode Island, U.S.A., by exfoliative vaginal cytology with confirmatory biopsy. The routine procedure consisted of a vaginal fluid smear aspirated from the posterior fornix, followed by a scraping from the external cervical os by a wooden spatula. Carcinoma *in situ* of the cervix was found in 148 (0·6 per cent), squamous cell cancer in 28, adenocancer of the fundus in 19, squamous cell cancer of the vagina in 6, and cancer of the ovary in 1. The youngest patient with cancer *in situ* of the cervix was aged 22. In 45 cases the diagnosis of malignancy would have been missed if the cervical scrape had been omitted. On the other hand the cervical scrape was negative in 9 cases in which the vaginal aspirate was positive. Both methods are therefore necessary. *F. J. Browne*

179. **The Application of Acridine-Orange Fluorescent Microscopy to Gynaecological Cytology.** (Die Akridin-

orange-Fluorochromierung in der gynäkologischen Zytodiagnostik.)

By E. Bontke, G. Kern and N. Schümmelfeder. *Geburtsh. u. Frauenheilk.*, **20**, 24–34, Jan. 1960. 8 figs. 1 table. 38 refs.

The technique of staining vaginal smears with acridine-orange (a modification of the method described by Bertalanffy) and their subsequent study under the fluorescent microscope is described. Smears were taken from 300 patients attending the University Gynaecological Clinic, Cologne; the smears from each patient were examined and compared using the Papanicolaou technique and the method described in this paper. The cytoplasm of cells rich in ribonucleic acid and acid muco-polysaccharides fluoresces red when examined under the fluorescent microscope after treatment with acridine-orange. Malignant cells have this characteristic, but from the authors' studies it is obvious that many normal cells have the same characteristics when examined by this technique. On the other hand, cells undergoing autolysis no longer fluoresce red and some carcinoma cells shed from the surface of a tumour are in this state. The authors therefore conclude that this technique is not suitable for use as a screening method for examining vaginal smears. The recognition of malignant cells in vaginal smears examined after treatment with acridine-orange demands as much experience as the orthodox staining techniques.

Peter J. Huntingford

180. **A Histochemical Study by Fluorescence Technique of the Epithelial Tumors of the Cervix and Uterus.**

By C. J. Louis. *Amer. J. Obstet. Gynec.*, **79**, 336–345, Feb. 1960. 1 table. 11 figs. 24 refs.

While normal tissues stain well with fluorescin-globulin stain, diminished affinity for this stain has been demonstrated in malignant cells. Differential staining is thus possible between normal and malignant tissues, and has been observed between tumour cells on the one hand and normal and hyperplastic cells on the other hand in a series of cases of carcinoma of the colon, epidermis, and breast, and in leukaemias occurring in man and animals.

The author has applied the method to a series of cervical erosions and to normal and malignant uterine and cervical tissues. He found that all normal tissues, cervical erosions and hyperplastic endometria associated with metropathia haemorrhagica fluoresced, while all malignant tissues, including adenocancers of the cervix and corpus uteri and squamous cell cancers of the cervix, failed to do so. In cervical cancers he observed tissues from the tumour as well as from the adjacent and histologically non-neoplastic areas.

The latter showed patchy areas of lack of staining composed of small groups of squamous cells similar to those in rats fed with carcinogenic compounds, and referred to as "islands of loss" because they constituted a pre-cancerous state, as was shown by the eventual development of frank tumours; similar areas have been seen in the skin, polyps of the colon and in the breast.

The value of this stain is not only to differentiate malignant from normal cells but also to distinguish hyperplastic from pre-neoplastic tissues. This would apply with special significance to carcinoma *in situ* of the cervix uteri.

F. J. Browne

181. **Cellular Changes in Vaginal and Buccal Smears After Radiation: An Index of the Radiocurability of Carcinoma of the Cervix.**

By H. W. Jones, B. Goldberg, H. J. Davis and B. C. Burns. *Amer. J. Obstet. Gynec.*, **78**, 1083–1098, Nov. 1959. 2 tables. 20 figs. 26 refs.

In a study of 68 patients with squamous cell cancer of the cervix treated by irradiation and followed up at least for 2 years, the authors have been unable to confirm the claims of Ruth Graham that it is possible to assess radio-sensitivity by the changes produced in normal vaginal cells found in smears after radiation.

They have now embarked on a study of radio-sensitivity of normal buccal mucous membrane cells by administering a dose of 1,500 r to the buccal mucous membrane. After 12 days a smear is examined and radio-sensitivity assessed by (*a*) an increase of over 25 per cent in smear cell area, (*b*) an assay of multinucleation, (*c*) decrease in the amount of desoxyribose nucleic acid per nucleus. So far the results are encouraging.

F. J. Browne

182. **Exfoliative Cytology During Pregnancy for Detection of Carcinoma of the Cervix.**

By H. J. Spujt, W. A. Ruch, Jr., P. A. Martin and J. E. Hobbs. *Obstet. and Gynec.*, **15**, 19–27, Jan. 1960. 1 table. 8 figs. 12 refs.

By the use of cervicovaginal smear, the authors discovered 7 cases of carcinoma *in situ* of the cervix among 3,352 pregnant women in the Washington University Obstetric Clinic.

Epithelial changes of atypical hyperplasia, ranging from focal to borderline for carcinoma *in situ*, were demonstrated in an additional 10 patients. Patients with atypical epithelium had cervical biopsies taken and if necessary a ring biopsy is taken later.

The authors believe that carcinoma *in situ* in the pregnant woman does not differ from that in the non-pregnant: nor does it regress post-partum.

J. G. Dumoulin

183. **Local Cytostatic Treatment of the So-Called Surface Carcinoma of the Cervix Uteri Testing Chemotherapeutic Effects on the Atypical Squamous Cell.** (Über Versuche der lokalen cytostatischen Behandlung des sogenannten Oberflächenkarzinoms am Collum uteri zur Prüfung der chemotherapeutischen Wirkung auf die atypische Plattenepithelzelle.)

By H. G. Hillemanns and D. Wagner. *Arch. Gynäk.*, **192**, 277–292, 1960. 11 figs. 12 refs.

The authors report the effects of treatment with a cytostatic drug on 4 patients suffering from carcinoma *in situ* of the cervix. Three of these patients were young, 31, 29 and 26 years respectively, and one was post-

menopausal (53 years). The diagnosis in all 4 cases had been verified by colposcopy, cytology and histology. An ointment containing 30 per cent Endoxan (made by "Asta-Werke", Brackwede, Westfalen) was used by vaginal application. In three of these four patients the lesions treated regressed completely. One of these patients had a lesion in an endocervical gland in addition to the changes on the surface of the cervix which remained unchanged. In the fourth patient there was initial improvement but the treatment had to be discontinued after half the dose had been given owing to severe side effects (leukopenia, continuous vomiting and poor general condition). Daily vaginal smears were taken from all patients. The atypical cells showed a tendency to maturation with corresponding changes in their nuclei and cytoplasm, especially a distinct acidophilic homogenization of the cytoplasm and regressive nuclear changes. Normal squamous epithelial cells also showed an accelerated maturation to acidophilic superficial cells. Serial sections after conization showed damage to the atypical cells similar to that seen after radiotherapy—inhibition of mitoses, breaking up of chromatin, cytoplasmic degeneration with vacuole formation—changes usually preceding cell death.

The authors think that the drug acted mainly through direct contact. When the blood supply to the vaginal mucosa was abundant in young mature women (and they assume this would be even more marked during pregnancy), absorption of the drug into the circulation took place causing side effects. In one case the side effects were severe enough to necessitate discontinuation of treatment. In elderly women with an atrophic mucosa no absorption and therefore no side effects were apparent, a fact which allows for higher dosage.

The aim of this paper was not to find a new treatment for carcinoma *in situ* in competition with the established method of conization, but to find a suitable way of testing the cancero-toxic effects of a cytostatic agent. An attempt at treatment of patients with invasive cancer using cytostatic drugs seems justified only if the efficacy of the agent has been proven on pre-invasive cancer cells.

Erica Wachtel

184. **Complications of the Urinary Tract Following the Treatment of Carcinoma of the Cervix by Irradiation.** (Komplikationsreiche Veränderungen am Harnsystem nach Strahlentherapie des Kollumkarzinoms.)

By A. KIRCHHOFF. *Geburtsh. u. Frauenheilk.*, **20**, 34–39, Jan. 1960 4 tables. 9 refs.

By systematic pre- and post-treatment examination of the urinary tract, using chromocystography and intravenous pyelography, Professor Kirchhoff has been able to assess the incidence of urinary tract complications related to the treatment of carcinoma of the cervix by irradiation. From 1952 to 1957, 1,145 cases of carcinoma of the cervix were treated in the University Gynaecological Clinic, Göttingen; the incidence of ureteric stenosis prior to treatment was 7 per cent, varying from 1·8 per cent of 386 patients in Stage I to 30·8 per cent of the 39 patients in Stage IV. Of 200 patients who were free from recurrence following treatment by irradiation, subsequent examination of the urinary tract showed that in 35 cases (17·5 per cent) there was some degree of hydronephrosis and in 13 of these only 1 functioning kidney. Twenty of these patients had no symptoms whatsoever, which were referable to the urinary tract.

Peter J. Huntingford

185. **Carcinoma of the Ovary.**

By M. E. GRIER and R. M. LANGDON. *West. J. Surg. Obstet. Gynec.*, **68**, 33–37, Jan.–Feb. 1960. 9 tables. 13 refs.

The 10-year results at St. Joseph's Hospital, Omaha, are reviewed. Forty-three patients had primary carcinoma of the ovary (14 per cent of the ovarian pathology) and their ages varied between 21 and 72, one half being between 40 and 55. About three-quarters of the patients delayed seeking advice even after the onset of symptoms and the results of treatment are poor. Helsel's clinical grouping gives a guide to prognosis, the only survivors after 5 years were in Groups I and II (8 out of 16), none of the 27 patients in Groups III and IV survived 5 years. The best chance is given by total hysterectomy with bilateral salpingo-oöphorectomy combined with excision of the omentum and followed by post-operative irradiation.

D. C. A. Bevis

186. **Malignant Pathology of the Remaining Ovary.** (Patologiá maligna del ovario restante.)

By G. DI PAOLA, H. L. GUIXA and J. E. OTTURI. *Obstet. Ginec. lat.-amer.*, **17**, 266–268. May–June 1959. 4 refs.

The authors examined the case histories of 110 patients suffering from malignant neoplasms of the ovaries, and found that 12 of them had previously experienced gynaecological operations.

Classifying their observations on the records of these 12 patients, they found that these could be grouped into three categories: (1) Five patients under the age of 40, in whom malignancy of the ovaries had become apparent in from 1 to 24 months after the operation. (2) Three patients, aged between 43 and 59, in whom the diagnosis had been missed at the time of the original operation. (3) Four patients who had remained well for many years after the original gynaecological operation.

The authors suggest that whilst it is desirable to leave the ovaries in young patients when the operation is being performed for an innocent condition in the uterus, these organs should be examined very carefully, and if any doubt exists, biopsies of them should always be taken in cases where they are not removed.

John F. Foulkes

187. **Endometriosis of the Vermiform Appendix.**

By R. E. LANE. *Amer. J. Obstet. Gynec.*, **79**, 372–376, Feb. 1960. 2 figs. 18 refs.

Endometriosis of the appendix should be considered in the differential diagnosis of right lower quadrant pain in the sexually mature female, but there are not any pathognomonic signs. The author describes 30 new cases

bringing the total number reported in the literature to approximately 200. The most frequent location was the subserosa and the mucosa was not involved in any.

The clinical features simulated acute or recurrent appendicitis; nausea, emesis, bloating, bizarre generalized abdominal pain, and right lower quadrant or pelvic pain not related to the menstrual periods may be present. In 4 patients there was also extensive pelvic endometriosis.

Right ovarian endometriosis was absent in 3 cases, which does not coincide with the view of Sampson that the ovary acts as an intermediate host for shed endometrial cells.

F. J. Browne

188. **Ureteral Obstruction from Endometriosis.**

By D. R. Brock. *J. Urol.* (*Baltimore*), **83**, 100–102, Feb. 1960.

Ureteral obstruction from endometriosis can be extrinsic or intrinsic. Only four cases of intrinsic obstruction have been reported and the author contributes a fifth. When extrinsic obstruction occurs treatment by castration usually causes the hydronephrosis to resolve except when irreparable damage has occurred. No case has been recorded of the treatment of intrinsic obstruction by castration.

In the case recorded a woman, aged 48, had complained of persistent dysuria for a period of months. No haematuria had occurred. Pyelography revealed hydronephrosis and hydroureter on the left side with obstruction at the left pelvic margin. A preliminary diagnosis of carcinoma or stricture was made. Ureterectomy was performed. The thickened area of the ureter measured 1·5 cm. by 0·5 cm.

J. H. Carver

OPERATIONS

189. **Results of Routine Prophylaxis with the Anticoagulant "Marcoumar" After Major Gynaecological Operations.** (Ergebnisse einer generellen Thrombo-Embolie-Prophylaxe mit Marcumar nach grossen gynäkologischen Operationen.)

By W. Soergel. *Zbl. Gynäk.*, **82**, 28–35, Jan. 2, 1960. 2 figs. 1 table. 8 refs.

In 1952 the author began to use routine anticoagulant prophylaxis in selected patients regarded as liable to post-operative thrombo-embolic complications. Having found that the selection in many cases was erroneous, in 1957 he introduced routine prophylaxis for all patients who had major gynaecological operations, except when it was contra-indicated.

He compares the incidence of thrombo-embolic complications between 3 chronological groups of patients:

(1) 990 cases operated before anticoagulants were used prophylactically;

(2) 1,000 cases in which anticoagulants were given selectively to about 20 per cent of the patients;

(3) 1,052 cases in which anticoagulants were used routinely with the exception of about 20 per cent.

The incidence of fatal embolism in the 3 groups was 0·51, 0·6 and 0·19 per cent. There were two deaths in the third group. One occurred in a patient who had not been given any anticoagulants, the other on the 5th post-operative day in a patient in whom the anticoagulant prophylaxis had only been started on the previous day.

Non-fatal pulmonary embolism occurred at the rates of 2·02, 0·6 and 0·57 per cent in the three groups. The incidence of deep venous thrombosis and of superficial phlebitis was 3·03, 1·5 and 0·95 per cent respectively. The total incidence of thrombo-embolic complications was 5·56, 3·7 and 1·7 per cent in the three groups.

The third group includes 842 patients who received prophylactic treatment with "Marcoumar". In 14 cases (1·7 per cent) haemorrhage followed which was attributed to the anticoagulant. Bleeding occurred from the vagina in 9 cases operated *per vaginam*; in 4 cases from an abdominal wound; and in one case in the retro-peritoneal space. Twelve patients responded to conservative measures including blood transfusion, but two patients died from massive haemorrhage. One death followed vaginal hysterectomy with removal of a myomatous uterus the size of a child's head; the other followed abdominal hysterectomy complicated by a large haematoma in the abdominal wall and anuria comparable to that seen in the "crush syndrome".

In spite of these complications the author advocates routine anticoagulant prophylaxis which should begin on the third post-operative day, using "Marcoumar". Heparin is used for the treatment of established embolism.

Bruce Eton

190. **Culdoscopy for Infertility: An Analysis of 203 Cases.**

By H. L. Riva, R. P. Hatch and J. L. Breen. *Amer. J. Obstet. Gynec.*, **78**, 1304–1308, Dec. 1959. 5 tables. 7 refs.

Several published papers have demonstrated the value of culdoscopy in disclosing unsuspected pelvic abnormalities in patients complaining of infertility. The authors report the results obtained in 203 cases examined under regional, local, spinal or caudal anaesthesia.

Unsuspected inflammatory disease, endometriosis, and Stein-Leventhal ovaries were found in 48, 26 and 5 per cent respectively. Rarer findings were bicornuate uterus, ovarian cysts, uterine fibromyomata and adhesions due to previous operations. The procedure was particularly rewarding in 82 patients in whom no abnormality could be found up to the time of the culdoscopy. Chronic inflammatory disease was found in 35 per cent and endometriosis in 30 per cent of this group. The pre-culdoscopy impressions were found to be wrong in 50 per cent. In 10 patients it was impossible to enter the peritoneal cavity, chiefly because of chronic inflammatory disease or endometriosis. In 2 patients the rectum was perforated.

F. J. Browne

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